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THE DEVELOPMENT OF A NEW BLOOD SUPPLY TO THE HEART BY OPERATION*

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Two relatively small arteries supply the most vital muscular structure of the body. This muscular organ is in constant motion, and to make its movements free and frictionless it is enclosed in a moist envelope of mesothelium. In providing man with this anatomic pattern Nature so frequently has deprived him of an important compensatory mechanism, namely, the ability to develop an adequate collateral blood supply to this organ. The heart is anchored in the body by the great vessels at its base, and while the entire surface of the heart is in direct contact with adjacent structures it has a minimum of direct continuity with the rest of the body. The only continuity that the heart has with the rest of the body is through the walls of the great vessels, some fat, a few nerves and lymphatics that constitute its anchorage, and these structures are relatively avascular tissues. This anatomic arrangement has made the heart a defenseless organ when its normal blood supply is interrupted. The appalling incidence of sudden death from heart failure attests to the destructive nature of coronary closure. Under normal conditions the myocardium receives practically all its blood through the left and right coronary arteries. The thebesian channels opening directly from the left ventricular cavity offer a second possible source of blood supply.[1] The importance of these channels has been the subject of argument. It has been claimed by some that the flow through the thebesian vessels is of little importance. This statement is based on the assumption that the thebesian channels are compressed, perhaps completely collapsed, by the tension of contracting muscle fibers during systole when the pressure in the ventricular cavity is being built up, and as these channels open during diastole the

* Some of the experimental data were presented in an address to the Caduceus Honorary Society of the Emory University Medical School on May 17, 1934.

pressure in the ventricular cavity synchronously falls. The third possible source of blood supply to the heart is through the extracardiac anastomoses that are present in the tissues at the base of the heart.[2] When the blood flow through the coronary arteries is reduced gradually, compensatory mechanisms are established. Complete closure of a major coronary artery is compatible with life, if the closure takes place sufficiently slowly. Indeed, complete closure of both major coronary arteries may be compatible with life,[3] but the number of times that the process of occlusion has gone on to completion in each of the two major coronary arteries is excessively small. The occlusion must occur at such a rate as to permit the other sources of blood supply to develop. Usually while this substitution is being made, life is snuffed out like a candle flame.

I have been interested in the heart as a surgical organ since 1923, and during this period of time a rather extensive background of surgical experimentation on the heart has been accumulated, as the result of over 1200 experimental operations which have been done by my assistants and myself. I made the observation several years ago that blood vessels extended between the heart and an adherent scar. At that time Dr. R. A. Griswold[4] and I were interested in studying chronic compression of the heart produced experimentally and we were trying to resect an adherent scar from the surface of the heart. In so far as these small vascular connections between the heart and adherent tissues were concerned, we simply noted their presence. At that time they had no other significance for us. Last November, while a compressing scar was being resected from a human heart, a broad band of scar extending from the base of the left ventricle to the parietal pericardium was transected. Brisk bleeding occurred from the cut ends of the scar and the bleeding was more brisk from the cardiac end than from the pericardial end. This was the first direct observation made at the operating table that blood actually flowed between myocardium and adherent tissues. This observation had now assumed new and additional significance because in the meantime we had been attempting to produce a collateral vascular bed to the heart experimentally. This observation confirmed our belief that vascular connections between heart and adherent tissues could be produced in the human being. I desire to give credit to Dr. Alan R. Moritz for directing my attention to the subject of vascularization of cardiopericardial adhesions. Moritz, Hudson and Orgain[5] not only demonstrated anatomically the presence of blood vessels in cardiac adhesions by the injection of carbon particles into the coronary arteries but also Doctor Moritz believed that under certain conditions these blood vessels might function and become an important source of blood supply to the heart. He directed my attention to a case reported by Thorel in 1903. This patient had complete obliteration of both major coronary arteries, and Thorel suggested the possibility of the heart receiving a supply of blood through adhesions that were present.

Could the heart be given a new source of blood supply by operation? I carried out the first experiments in an attempt to study this problem in

February, 1932, and shortly thereafter Dr. V. L. Tichy collaborated with me, not only in the technical surgery that was involved but also in the solution of many problems.[6] Doctor Moritz followed the work with interest and gave us valuable suggestions concerning the injection and study of the specimens.[7, 8] In these experiments the collateral vascular bed consisted of parietal pericardium and pericardial fat. The epicardium and the lining of the parietal pericardium were removed with a burr because it was our belief that these structures acted as a barrier to the growth of blood vessels into the heart. The results of these experiments were as follows: (1) Almost total occlusion of right and left coronary arteries near the aorta was compatible with life if the heart had been provided with a collateral vascular bed. The occlusion of arteries was produced by silver bands which were compressed in stages at repeated operation. (2) Dye penetrated the myocardium through the collateral bed, and we assumed that if particles of dye entered the myocardium as freely as they did, that blood also flowed into the myocardium through these vascular channels. We believe that we succeeded in giving the heart a new source of blood supply and that this was sufficient to maintain cardiac function. (3) A pressure-differential was necessary to promote anastomosis between the cardiac and extracardiac vascular beds. In other words, a physiologic need for blood in the myocardium was necessary for such anastomoses to develop. The physiologic need for blood was produced by occlusion of the major coronary arteries by silver bands which were placed around the arteries and which were compressed in stages at successive operations. (4) The development of anastomoses between the myocardium and the collateral bed was demonstrable three weeks after operation. More recently we have succeeded in demonstrating anastomoses between extracardiac and cardiac beds two weeks after the bed was applied to the myocardium.

During the past eight months additional experimental operations have been carried out with the assistance of Dr. Ernest Bright and Miss Alice B. Maltby. In these experiments pedicle grafts of muscle were used together with the pericardial and mediastinal fat for the vascular bed. Omentum was also brought up through an opening in the diaphragm and sutured to the heart. These experiments have not yet been published but I shall refer briefly to some of the results:

(1) Anastomoses readily develop between skeletal muscle and cardiac muscle provided the normal blood supply to the heart has been reduced. If the coronary arteries were not partially occluded the anastomoses between omentum or skeletal muscle and myocardium, although present to some extent, did not become well developed.

(2) A collateral vascular bed gives the heart partial, but not complete, protection when the right coronary artery is occluded in one stage. When the descending ramus of the left coronary artery is ligated in one stage, the degree of protection afforded by a collateral vascular bed is slight. The conclusion that can be drawn is that a collateral vascular bed protects the heart when the right coronary artery is occluded in one stage. The larger

the coronary artery occluded, the less is the protective effect. The evidence, however, was definite that the presence of a collateral vascular bed protected the heart from the ravages of sudden occlusion of a major coronary artery. In this respect the operation becomes a prophylactic measure, and if the experimental data can be applied to patients with coronary sclerosis it would seem that this operation should be done early in the course of the disease, before replacement of myocardium by scar tissue and fat has taken place or before the heart has been brought to a standstill by occlusion.

(3) The right coronary artery, the ramus descendens of the left coronary artery, or the ramus circumflexus of the left coronary artery, can be ligated successfully almost as a routine if the ligation is carried out in two stages.

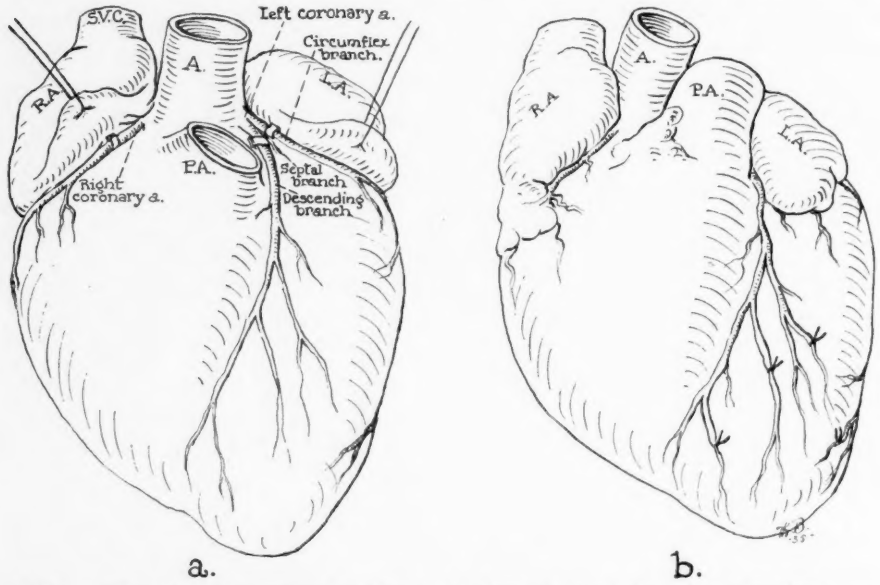

FIG. 1.—Two types of operations are shown: (*a*) shows the usual sites where silver bands were applied to the coronary arteries. A reduction of 30 to 50 per cent in the cross sectional area of these three arteries was compatible with life. (*b*) shows another type of experiment. Four or five peripheral branches of the coronary arteries over the apex of the heart were ligated. This experiment was always fatal. In (*a*) the reduction in total coronary blood flow was considerably greater than in (*b*). The heart cannot tolerate ischemia of a severe degree even though the area of ischemia is small. The collateral bed produced by operation can transport blood to such ischemic areas.

The explanation for this is that the reduction in blood flow brought about by the partial constriction of this vessel—and as little as 20 per cent of the cross section is efficacious—is compensated for by the development of collateral vessels. After this compensatory mechanism has been established, complete occlusion of the artery does not produce complete ischemia of the muscle. The myocardium remains viable after complete occlusion and additional channels become established.

(4) Distribution of blood to every part of the myocardium is of vital importance. If one relatively small portion of the myocardium is rendered ischemic by the peripheral ligation of four or five arterial branches, ventricular fibrillation develops and this is routinely fatal (Fig. 1). An equal

distribution of blood to the myocardium is essential for maintenance of function.

(5) The collateral vascular bed is functional not only in making a new source of blood supply available to the heart but it also helps to distribute blood to various portions of the myocardium. In this respect the collateral vascular bed produced by operation acts as an anastomotic bridge that transports blood from the bed of one coronary vessel to the bed of another coronary vessel where the blood flow is deficient.

The question naturally arises as to whether or not the presence of the new vascular bed might interfere with the movement of the heart. The importance of adhesions to the heart has been greatly overemphasized in the past. Cardiopericardial adhesions usually are silent lesions of little or no clinical significance. In none of our experiments did we find that the circulation was in any way embarrassed by these adhesions. Adhesions to the heart can embarrass the circulation in several ways: (1) A constricting bed of scar tissue may produce chronic cardiac compression. Adhesions in this clinical syndrome are entirely incidental and of no significance. (2) Adhesions between the heart and chest wall may act as a harness through which the heart pulls and expends energy. In our experiments the heart was not so extensively and intimately bound to the chest wall as to produce embarrassment. (3) The heart may be sharply angulated from its normal axis by such adhesions so that it cannot effectively function.

With this experimental work as a background it was decided to attempt to apply the data to a patient suffering from coronary sclerosis. To select a satisfactory case was not without difficulty and then to have the selected patient give his consent to have an operation performed on his heart (an operation that had never been done before on a human being) required something of the heroic spirit. For this reason I wish to mention the name of the patient, Joseph Krchmar, of Chardon, Ohio. I believe he has made a contribution to surgery. I also want to give credit to his physician, Dr. Walter Corey of Chardon. Doctor Corey had the imagination to see the possibilities of the experiments and he made a serious attempt to secure a patient for the operation. I also want to thank the internists, Dr. Joseph T. Wearn and Dr. Harold Feil. Doctor Feil is collaborating in the clinical aspects of this work.

Case Report

J. K. was admitted to the Lakeside Hospital February 3, 1935. He was 48 years old, a white male, married, formerly a coal miner, more recently a farmer. His complaint was pain in the chest, over the heart, to the left of the sternum. He remembers the onset of the pain distinctly. A sharp pain appeared suddenly over the heart while he was at work nine years ago. It was accompanied by dyspnea and dizziness. After this initial attack he went back to fairly heavy labor until five years ago. Then, because of repeated attacks of substernal oppression, he moved to a farm. The precordial oppression was accentuated after meals. The patient claims that he had not done heavy work for the past five years, but he has done such things as plowing. During the last year or two he suffered from attacks of sharp, knife-like pains over the heart. These radiated to the left shoulder and down the left arm to the elbow. During these attacks of pain

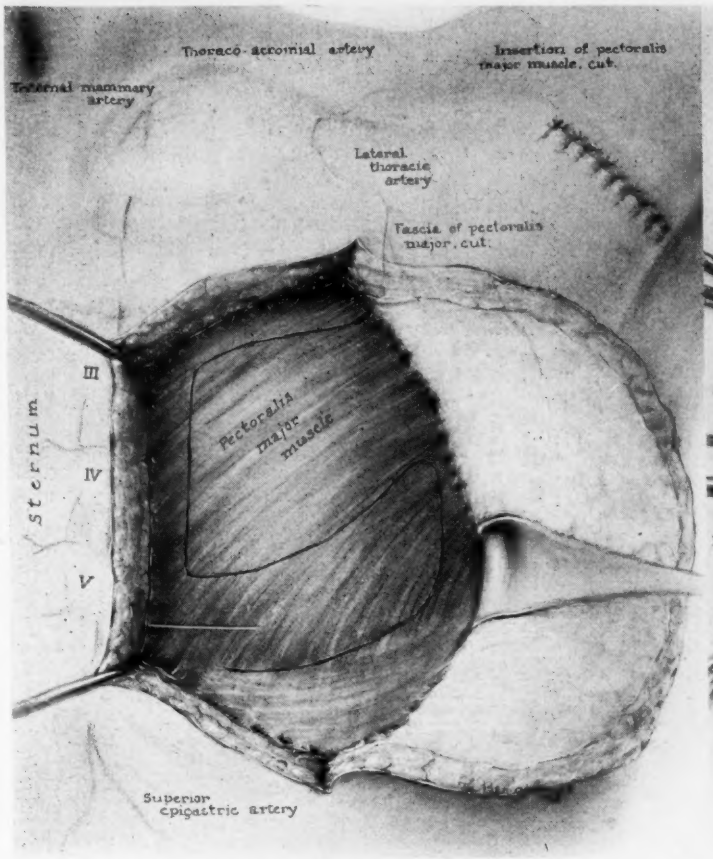

FIG. 2.—The insertion of the pectoralis major muscle was incised. A flap of skin and pectoral fascia was turned laterally. The pectoral muscle was incised as shown. This provided a pedicle graft of muscle with its attachment lateral to the sternum.

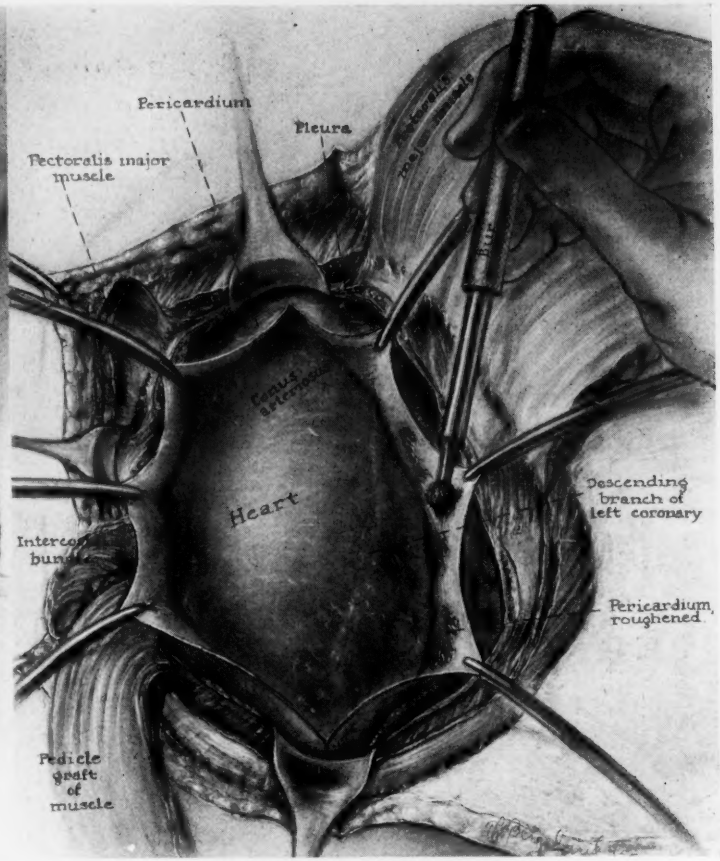

FIG. 3.—The pericardium was opened. The inner surface of the pericardium is roughened with a burr.

mary vessels onto the surface of the heart.

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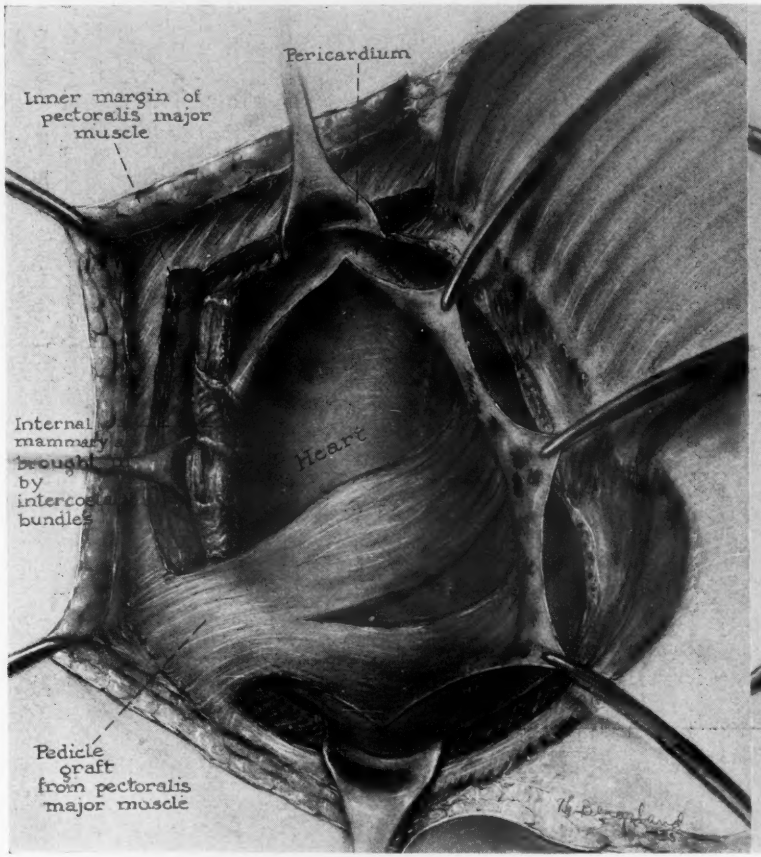
Pericardium
Inner margin of pectoralis major muscle
Internal mammary brought by intercostal bundles
Heart
Pedicle graft from pectoralis major muscle

FIG. 4.—The pedicle grafts were carried posteriorly to the circumflex bed and sutured to the parietal pericardium. The intercostal bundles were carried beneath the sternum and sutured to the parietal pericardium. This carried the internal mammary vessels onto the surface of the heart.

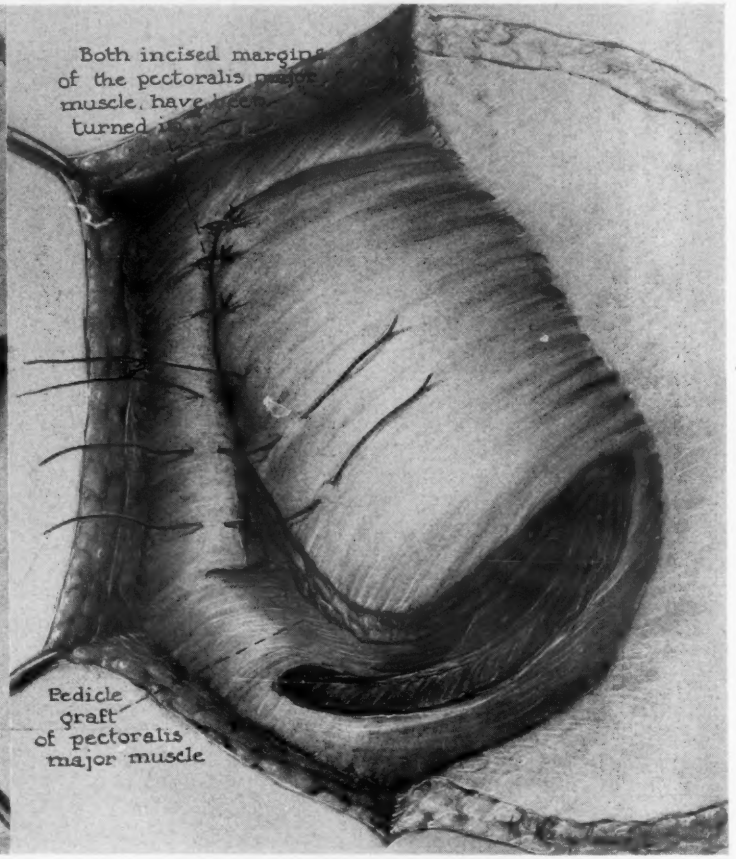

FIG. 5.—The parietal pericardium was left open and the incised margins of the pectoral muscles were inverted so that they came into contact with the heart.

he felt suffocated, was dyspneic and the heart palpitated. Epigastric distress after meals was also a prominent symptom. Numbness and tingling of the left hand and fingers frequently accompanied the pain. Ten days before admission to the hospital the patient, while carrying some wood into his house, was seized with violent, sharp, precordial pain, dyspnea and dizziness. He went to bed where he remained until he came to the hospital.

The patient was well developed, well nourished and of a phlegmatic temperament. His expression was worried. Examination of the precordium was negative. The heart was slightly enlarged to the left. On admission to the hospital the systolic pressure was 155 and the diastolic pressure was 95 Mm. Hg. The peripheral arteries were moderately thickened and tortuous. Exercise produced substernal oppression but no sharp pain. The electrocardiogram after exercise showed no significant change. While in the hospital the

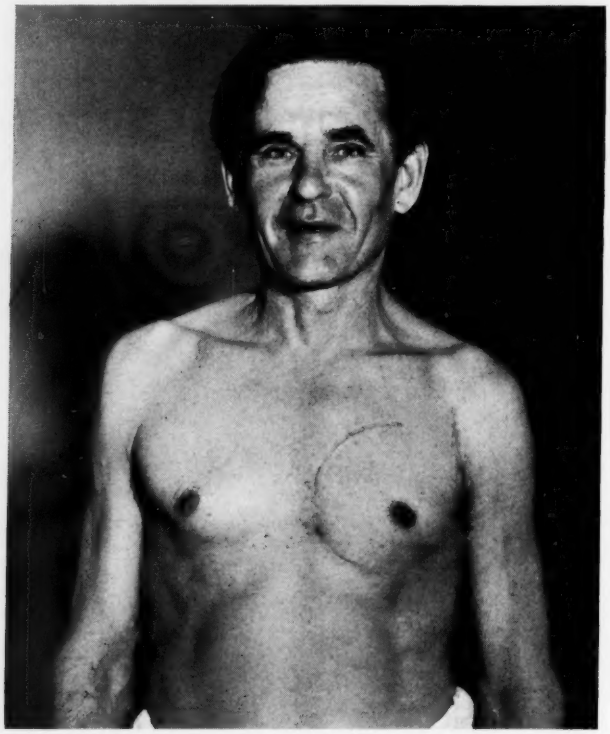

FIG. 6.—Patient three and one-half months after operation.

patient suffered a sudden, severe, knife-like attack of pain after taking a bath. The pain was precordial, to the left of the sternum, and did not radiate. At the same time he became cyanotic, very dyspneic and extremely apprehensive. Amyl nitrite gave him relief. A diagnosis of coronary sclerosis and angina pectoris was made. The electrocardiographic findings would indicate that there was no bundle damage thus far. He also had generalized arteriosclerosis and a mild degree of hypertension.

The patient consented to operation. He desired to go home to visit with his family but he returned to the hospital at midnight because of pain and a fear of impending death.

Operation.—February 13, 1935. Gas-oxygen anesthesia was used. The insertion of the left pectoral muscle was incised at the suggestion of Dr. W. C. McCally, for the purpose of mobilizing this muscle. This wound was closed. A curved incision was then made to the left of the sternum. (Fig. 2). The fascia was dissected from the left

pectoral muscle. The inferior portion of the pectoral muscle was incised for the purpose of making a pedicle graft. An incision was then made through the pectoral muscle parallel to the sternum exposing the third, fourth, and fifth costal cartilages. The muscle was freed from the chest wall. These cartilages were removed. The intercostal bundles were cut laterally leaving them attached to the region of the internal mammary vessels. The pericardium was incised from base to apex (Fig. 3). The lining of the pericardium everywhere was roughened by means of a burr. The epicardium was removed in shreds by means of a burr. This produced a great many extra systoles and some dilatation of the heart. Rest periods were given. At the suggestion of Doctor Wearn I tried to palpate the coronary vessels but with the heart moving I could not be sure that I could feel them. The pedicle graft was then divided longitudinally and both pedicles were swung around to the circumflex area of the heart. These grafts were sutured laterally and posteriorly to the parietal pericardium (Fig. 4). The intercostal bundles and the medial margin of the pectoral muscle were carried beneath the sternum and attached to the parietal pericardium. These structures carried the internal mammary artery onto the surface of the heart. The lateral margin of the pectoral muscle was then inverted so that the incised surfaces were in contact with the heart (Fig. 5). The fascia of the pectoral muscle was sutured; the skin was closed. The wound was not drained.

Three and one-half months have elapsed since the operation (Fig. 6). The patient has been kept in the hospital during this period but during the last six weeks he has been doing light work, such as serving trays, moving beds, *etc.* For several weeks after operation he had indigestion after meals. This has disappeared. He claims that he has no precordial pain; that the feeling of oppression over the heart has disappeared, that he has no sharp radiating pains to the shoulder and arm. He claims that he is well. He can exercise without pain, although up to the present time he has done no hard physical work. I have emphasized the importance of describing accurately what symptoms he has, but to me and to everyone else who talks with him he claims that he is better. Objectively I can say that he appears to be better. The worried expression has left him, and he has a fine spirit.

SUMMARY

The heart can be given a new blood supply experimentally. On the basis of this work a collateral vascular bed to the heart should offer some benefit to patients suffering from coronary sclerosis. A collateral vascular bed was given to a patient with coronary sclerosis on February 13, 1935. Three and one-half months after operation the patient claims that he has been greatly benefited. However, it will be necessary to have a number of such results before we can attach any clinical significance to this operation. I want to emphasize the point that the work is still in the experimental stage and I do not recommend the performance of this operation until it is established by operation upon a number of patients.

ADDENDUM: September, 1935. Seven months have now elapsed since the operation on the first patient. He continues to work as a gardener; he has no pain and he claims that he is cured. I have carried out the operation on five additional patients, making the total number seven. The third patient had an extremely marked degree of arteriosclerosis. At the operating table I could palpate the ramus descendens. It was hard, tortuous and several millimeters in diameter. The patient had been incapacitated sine 1942. One and one-half years ago a total thyroidectomy was done. He has kept his basal metabolic rate at about minus 20 by taking thyroid extract. His life had been of a vegetative nature,

spending as he did 20 hours a day in bed. Two and one-half months have elapsed since we did the cardiac anastomosis. He states that he is completely free from all pain and discomfort. He is able to take twice the dose of thyroid extract that he took before the operation and his basal metabolic rate is plus 2. He is up and about six to eight hours a day and his interest in life has returned. He is still an invalid and he is still weak, but the complete absence of pain, his normal basal metabolic rate, his increased activities and interests, are facts that may be of real significance in establishing the operation as a beneficial procedure. The fourth patient is a well known surgeon from Ashland, Kentucky, who came to me because he believed in the soundness of my operation. He had suffered a myocardial infarct with dilatation and failure. He also had diabetes mellitus. He believes that he has shown some improvement but the pulse rate on occasions becomes rapid and he has had several attacks of anginal pain since operation. A sufficiently long interval has not elapsed to comment on the other cases. These cases will be reported by Dr. Harold Feil and myself.

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DISCUSSION.—DR. JOHN B. FLICK (Philadelphia, Pa.).—The experimental work of Claude Beck, in establishing a collateral vascular bed in the myocardium of animals and thus protecting the myocardium from anoxemia due to coronary occlusion, furnishes an entirely new avenue of approach in combating cardiac ischemia due to coronary artery disease in human beings.

Sir Thomas Lewis says, "The malady originally described by Heberden under the term angina pectoris is one in which pain of characteristic type occurs during effort. It is by far the commonest form of malady in which angina pain occurs. The pain may be interpreted as resulting when the blood supply to the heart, or part of the heart, is limited and consequently inadequate when the heart is called upon to do work at a certain increased rate—a condition of relative ischemia."

The operative treatment of angina pectoris first proposed by Francois Frank in 1899 and first practiced by Jonnesco in 1916 was purely symptomatic and was not intended to eradicate the disease. The surgical act aimed at division of the nervous arc thus preventing the patient from recognizing the symptom pain (Elliott C. Cutler). Since then various neurosurgical procedures along similar lines have been devised for the relief of cardiac

pain and practiced with more or less success, but they have not gained greatly in popularity, possibly because of technical difficulties and possibly because of the uncertainty of the results.

Removal of the normal thyroid gland in the treatment of heart disease was proposed by Blumgart, Lavine and Berlin and was practiced for the first time on December 14, 1932, at the Peter Bent Brigham Hospital in Boston. Strikingly beneficial results from this operation have since been obtained in the group of patients suffering from angina pectoris. The rationale of this procedure for the treatment of heart disease has its basis in the reduction of the metabolic demand on the heart by the total ablation of the thyroid gland.

Beck's operation strikes directly at the myocardial ischemia and theoretically should be beneficial where the ischemia is due to organic changes in the walls of the cardiac vessels. Experience alone can determine the place in surgery of Beck's ingenious and logical operation and he is to be congratulated upon a fine piece of work which at least has proved that a collateral circulation can be established experimentally in the myocardium of animals.

DR. ELLIOTT C. CUTLER (Boston, Mass.).—I should like to be among those who congratulate Doctor Beck upon what I know to be the end-result of a vast amount of work and a most ingenious investigation.

This morning our President spoke of our job as one of keeping Nature from taking us away before our time, but I wonder whether we should apply our energies to people as young as forty, as suggested by Doctor Cheever. I had the opportunity to see Doctor Beck's first patient as he was recovering from the operation and the ordeal did not seem unusual.

It is certain that the attack proposed by Doctor Beck and the physiologic background for this procedure are much more admirable, much better suited and far more certain to hold hope for ultimate good than any procedure yet proposed for those cardiac disorders that have as beginnings and cause ischemia of the myocardium.

Whether one is to turn in muscle flaps which many of us have tried in other conditions without much success, whether one is to use the fat about the pericardium, or whatever the actual method of establishing the collateral circulation is to be, it is certain that the understanding of what seems necessary and which Doctor Beck has attempted to carry out in these experiments constitute the most logical attempt that has ever been suggested.

The difficulty, of course, is going to be the same as we all have found in other conditions, now that ingenuity of the surgeon has brought us so far apace, *i.e.*, to convince our medical colleagues that our undertakings are desirable, or perhaps educate them to help us choose which case is desirable for the definite procedure.

Knowing how in this country surgery of the pericardium has lagged behind such surgery elsewhere, partly because of the attitude of our internists, one can imagine the difficulties in this field of choosing the proper case of arteriosclerotic heart disease, angina or hypertensive heart disease, as the one best suited for such procedure. I have no doubt if Doctor Beck keeps at it, and he fortunately has a group of medical colleagues who are interested and will help him, he will be able to tell us in a few years which form of heart disease is best suited and most likely to be relieved by this procedure.

I think we should all congratulate him sincerely for an admirable piece of work.

DR. W. F. RIENHOFF, JR. (Baltimore, Md.).—Independently and without any knowledge of Doctor Beck's experiments, or interest in this problem, we

began in October, 1934, investigating different methods of supporting an interrupted coronary circulation. We have used a series of old dogs for the reason that the independent development of a collateral circulation in younger animals is so readily achieved that recovery from ligation of the right or left anterior descending coronary artery may be clinically uneventful and easily survived by the animal. Doctor Beck did not state whether his series of dogs were young or old. In the older dogs, in our experience, ligation of the left anterior descending branch of the left coronary artery almost always resulted in either ventricular fibrillation or a marked arrhythmia. Ligation of the left coronary artery before departure of the circumflex resulted invariably in ventricular fibrillation. In a small series of nine dogs, Dr. E. Cowles Andrus, Dr. August Jonas and myself obtained electrocardiographic studies before beginning the experiment, and used only those animals in whom the electrocardiograms were normal. Under ether anesthesia, an incision was made in the fifth interspace on the left side exposing the pericardial sac which latter was opened. The central tendon of the diaphragm was then incised and the omentum drawn up into the left thoracic cavity. The epicardium was then moistened with half strength iodine and the omentum wrapped, so to speak, completely about the heart, entirely covering the anterior surface. To insure maintaining this position the omentum was fastened to the epicardium by two interrupted fine silk sutures. The pericardial sac was not closed but the hiatus in the central tendon of the diaphragm was pulled snug about the omentum. After this cardio-omentopexy had been performed, Doctor Andrus found the type of electrocardiographic curve present, suggested a coronary occlusion. Whether this alteration in the electrical reaction of the dog's heart was due to the small amount of iodine painted on the epicardium or whether it was due to the two stitches placed in the heart wall, away from the coronary vessels, was not determined. Three to six weeks later, ligation of the entire left coronary artery just below its origin from the aorta and above the division into the left anterior descending and circumflex arteries was accomplished by taking a deep bite with a French No. 2 needle in the ventricular wall in the region of the left coronary artery just beneath the tip of the left auricle. The distension of the coronary veins distal to the ligature proved its location. No disturbance in cardiac rhythm followed these ligations after previously performed cardio-omentopexy, either clinically or in the electrocardiogram. The dogs were not at all ill and were up and around their cages the next day. Whereas before similar ligation was invariably fatal, not one animal succumbed after adhesion of the omentum to the heart had been produced. At the second operation extensive adhesions were revealed to have occurred between the omentum and the heart wall. These bled profusely when slightly separated. The electrocardiograph remained the same following the first and second operative procedures. In other words, ligation of the entire left coronary vessel in this series of old dogs was relatively inconsequential when the coronary circulation was properly supported by an outside source of blood supply. We are in the process of sacrificing and injecting our specimens. Carmine gelatin was used for the coronary circulation, being injected in the aorta. This solution will not go beyond the arterioles and thus will not fill the capillary bed in the myocardium. No injection mass entered the cavities of the heart and therefore the thebesian vessels were not injected. Prussian blue mass was injected into the celiac axis, thus filling the omental vessels. This mass will fill the capillary bed and in the as yet incompletely cleared specimens, seems to have penetrated the capillary branches of the coronary system.

These specimens will be reported on later. We have not entertained the hope that this procedure of cardio-omentopexy will be clinically applicable except possibly in such cases of coronary thrombosis that might be seen at an early stage of the interruption of the coronary circulation.

DR. J. SHELTON HORSLEY (Richmond, Va.).—Is there not some difference between the circulation of the blood from the omentum and that from the pectoral muscle? According to the procedure described by Doctor Beck the pectoral muscles were severed near their insertion, and a portion of the muscle turned onto the heart. This would, of course, involve destroying the nerve supply to the pectoral muscles, with consequent atrophy of the muscle and diminution of its blood supply, even if no vessels had been actually injured when the muscle was divided. The omentum, however, when brought up to the heart would suffer no trophic changes, and consequently circulation would not be impaired by such conditions as beset the pectoral muscles when they are divided near their insertion.

DOCTOR BECK.—The second patient upon whom we carried out our operation died one week later. A thrombus developed at the bifurcation of the aorta and occluded the left common iliac artery. The ischemia of the leg was very painful and the patient died within several hours. The thrombus developed at the site of an atheromatous ulcer of the abdominal aorta. The coronary arteries showed extensive and marked sclerosis. The right coronary artery was completely occluded about 14 Mm. from its ostium. The lumina of the ramus descendens and of the ramus circumflexus of the left coronary artery were markedly constricted but not completely occluded. The myocardium of the right ventricle showed extensive replacement by fat. There was no evidence of infarction in the left ventricle. The pedicle grafts of skeletal muscle and the adjacent fat and pericardium were adherent to the myocardium and for the present at least I am satisfied with this part of the operation.

In our experience ligation of the ramus circumflexus of the left coronary artery in one stage had a high mortality, even though a collateral vascular bed had been provided for the heart. Ligation in two stages is usually successful. This statement applies to the right and to either major branch of the left coronary artery.

The pedicle grafts of skeletal muscle brought in from the chest wall are deprived of some of their normal blood supply. We know, however, that the body has a great capacity to develop blood vessels and in our experiments we obtained excellent anastomoses between the vessels of cardiac muscle and of skeletal muscle. We used omentum in a number of experiments. Anastomoses between the coronary bed and the vessels of the omentum can be obtained. I am doubtful whether omentum could be used on a human patient because the opening in the diaphragm complicates the operative procedure. Experience may alter this point of view.

TRAUMATIC CARCINOMA OF THE BREAST

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WHEN statistics of carcinoma of the breast in which trauma is alleged to be the cause, vary from 6.8 per cent (Rosenstein) and 7.3 per cent (Guleke) to 37.9 per cent (Sprengel) and 44.6 per cent (Williams), it is evident that the value of these statistics as proving or disproving the traumatic origin of breast cancer is very small. Even statistics on relatively large numbers, by which it might be hoped to eliminate other factors, show similar if smaller variation. Ziegler, in 170 cases, found 37, or 22 per cent, to be due to alleged trauma. Loewenthal, in 934 cases found 135 or 13.4 per cent and H. Snow, in 9,600 cases of carcinoma of the breast found 11.5 per cent to have a supposedly traumatic cause. These figures average a little less than 12 per cent.

It is very unusual for a person not to be able to recall some more or less remote injury to the breast in which carcinoma has been found, such as striking it against the edge of a bedroom door in the dark, slipping in the bathtub or on a rug, the breast striking a chair or other piece of furniture, perhaps more frequent than all, a blow by someone's elbow in a jostling crowd or a vicious kick by a child carried in the arms. Often in such cases the carcinoma is discovered when patient goes to the doctor because of the bruise, and the doctor finds the tumor too large to have grown in the interval following the trauma, the injury serving merely as the occasion of the discovery of the carcinoma.

For these and other reasons, pathologists and clinicians are skeptical of the allegation that trauma may cause carcinoma in a normal breast. Perhaps the case is a little better for chronic or repeated traumata than for a single blow.

Manifestly, from the nature of the case, it is impossible to prove the proposition, but what can be done, and it would seem to be worth while, is by collecting a sufficiently large series of presumptive cases which, verified as to the nature, severity and date of the trauma, date of discovery of the carcinoma, histologic character of the growth, *etc.*, to arrive at a fair estimate of the probabilities in the premises.

There is real need for such an authoritative statement of probabilities for use in legal decisions, particularly in industrial accident and workmen's compensation relations.

Various criteria have been put forward in this connection, but it is difficult to satisfy all of them.

1. A definite injury of considerable severity.
2. Development of tumor at the injured spot.
3. In the case of the breast, a tumor which histologically is of a known form of breast tumor.

4. Tumor discovered three weeks or more after the accident (German practice), and then should not be larger than likely to have grown in the interval following accident.

5. Absence of tumor at the site of injury before the accident. This last would be of great value in the determination, but may not be regarded as a *sine qua non,* for only rarely would a person be examined, even for life insurance, with sufficient thoroughness.

The case herewith reported fulfils all the above conditions except the last. It is published for its value as a case of carcinoma of the breast presumably caused by a single blow on the gland.

This case has been given an unusual amount of study, and while there are several hiatuses in the record, the conclusion is all but irresistible that the trauma was the probable cause of the subsequent carcinoma. Moreover, the case presents a number of unusual conditions, themselves worthy of record.

Case Report

E. S., just under 17 years of age, was commandeered with others in his town to fight a forest fire. On September 22, 1928, running down hill to avoid the fire, he stumbled and fell down a bluff, striking his right breast violently on a tree stump, one and one-half or two feet high. The breast became swollen at once but when pain and soreness persisted, the boy feared that he had broken a rib, and only on the seventh day first consulted a physician, who "found the breast swollen to the size of half a grapefruit, red, hard and discolored, the skin over the upper central part of the breast abraded, the areola and nipple also injured. Temperature 101°. Nodes in both axillae somewhat enlarged, presumably from the abraded areas being infected. Roentgenography showed no fracture of rib. Under ultraviolet irradiation and hot applications the swelling gradually went down, and as the abrasions healed, the axillary swelling disappeared. In a few weeks the breast became normal except for a knot, the size of a chestnut, directly under the nipple which would not absorb." The patient was discharged as ready to return to work on November 16, 1928, nearly eight weeks after the accident.

On November 25 he again consulted his physician because the swelling was growing, and by February 1, 1929, it was "as large as half a lemon, being conical with diameter at the base of almost two inches causing dimpling of the skin when moved." It was also slightly tender. The doctor, fearing it was carcinoma, sent patient to a surgeon, who described the growth as of "about the size of a silver dollar, hard, leathery, about one-quarter inch thick, of very firm consistency, its center a little above the nipple. The skin is freely movable over the mass and it is freely movable over the pectoral muscle." He considered it potentially malignant, and advised its removal.

On March 5 the surgeon removed the entire breast subcutaneously through an incision around the lateral inferior border, but did not investigate the axilla. He looked at the growth after removal, found it yellowish in color; said it had no resemblance to carcinoma even on section; that it was "just a fibrous mass, the result of mastitis, as he had removed from the male breast in a number of instances," and threw the tissue away!

Two and one-half years later (November 25, 1931) he was again consulted because of the appearance of a painful lump in the opposite (left) axilla. Axillary nodes the size of pigeon eggs, some also at base of neck. Blood examination: Red cells 5,000,000; leukocytes 9,200, 65 per cent polymorphonuclears. No injury nor abrasion of hands; patient did clean some rabbits in November—no sign of general infection.

An axillary node was excised (February, 1932) and examined by the late Dr. W. Ophüls, pathologist of Stanford Medical School, who pronounced it metastatic carcinoma.

FIG. 1.—Left side of neck, left arm and the entire trunk edematous.

FIG. 2.—The skin of the trunk, more so on the left side, was filled with myriads of small tumors visible only by tangential illumination.

Claim was made by the patient and his family against the State Compensation Insurance Fund and the matter brought before the Industrial Accident Commission of California. The record was examined by a number of surgeons on behalf of the Commission with varying opinions as to the industrial nature of the carcinoma. The patient, doing badly, was brought to San Francisco and put under my care on August 17, 1932. He then complained of shortness of breath but felt encouraged because he was gaining in weight.

On examination patient was seen to be a tall, well built young man of 20, pale and in evident distress. Left side of his neck, left arm and the entire trunk edematous (Fig. 1). Both sides of the chest dull, moderate ascites, hence the gain in weight. The skin of the trunk, more so on the left side, was filled with myriads of small tumors, palpable but visible only by tangential illumination (Fig. 2). Temperature 99°; pulse 96; respiration 24. Wassermann negative. Red cells 5,545,000, reticulocytes 9.9 per cent; hemoglobin 100 (Sahli), leukocytes 13,150, of which 86 per cent were polymorphonuclears, 17 per cent banded, 69 per cent segmented; platelets 229,395.

Roentgenologic examination of the chest showed pleural effusion and pericardial distension, but no bony metastases. Biopsy of one of the skin nodules showed carcinoma, its cells filling the lymph spaces of the skin.

The dyspnea rapidly increased in the next day or two. On August 24 1500 cc. of clear fluid was removed from left chest, with but little improvement in the respiration. Two days later when preparations were being made to aspirate the pericardium, patient suddenly died.

Autopsy by Dr. J. B. McNaught, assistant pathologist, Stanford Medical School, showed the immediate cause of death to be an hemopericardium, the blood having evidently come from a slow oozing pericardial metastasis. Fluid in both pleural cavities; metastases in the lymph nodes of each axilla, on the right with necrotic centers, therefore presumably older than on the left. Metastases numerous in the mesenteric and mediastinal lymphatics, but almost none in the liver, spleen, lungs, heart and kidney. There were lymphatic metastases in the tissues about the prostate but no tumor found in the gland itself.

A remarkable feature of the case was the widespread occurrence of metastases in the lymphatic system, particularly in the skin of the trunk, in fact everywhere except in the skin and subcutaneous tissues of the right breast, the site of the surgical operation.

Most meticulous search by the pathologist failed to find any tumor which could be considered primary. Histologically, the tumors all over the body were identical and consisted of large epithelial cells, sometimes arranged in gland-like order, the arrangement being such as to suggest origin in the breast and in no wise resembling intestinal glands.

It seemed to me highly probable that the case was a result of the injury to the right breast three years before, and I so reported to the Industrial Accident Commission, accounting for the failure of the tumor to appear in the skin of the right breast by the fact of the operation having blocked the lymphatics. The wide dissemination of the lenticular metastases in the lymph spaces of the skin (Fig. 2) is sufficient answer to the claim made in defense that cancer of the breast is not likely to appear in the lymph nodes of the opposite side. It also seemed probable that the inflammation which followed the abrasions perhaps also the hematoma which resulted from the injury contributed to the blocking of the lymph channels through the right axilla, but since the lymphatics of the opposite axilla were also blocked, it may be that the size of the

cancer cells was the chief circumstance which prevented the carcinomatous elements being poured into the blood stream. It was certainly remarkable that the tumor appeared not to have been disseminated through the blood stream but almost exclusively through the lymph spaces and lymphatic vessels.

The responsibility of the decision was such that I asked that the record and sections be submitted to Dr. James Ewing of New York. After much study in his laboratory, and debate, Doctor Ewing replied as follows: "This case has been extensively discussed by our staff, and we feel that there is no escaping from the conclusion, that in all probability, if not with reasonable certainty, this boy presents a genuine case of traumatic mammary cancer. The lack of sections of the original tumor, and of knowledge of the previous condition of the breast, can hardly balance the very striking evidence of the traumatic origin, indicated by the very clear clinical history. It is a most remarkable case, and it should be recorded."

The record and correspondence being reported to the Industrial Accident Commission, they decided in favor of the family.

SURGICAL SIGNIFICANCE OF ENDOMETRIOSIS

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ENDOMETRIOMA is one of the many names at present applied to tumors containing endometrium or tissue resembling endometrium, and which respond to the same stimuli as those which affect normally situated endometrium. These tumors are recognized much more frequently now than formerly. There is no doubt that many of them cause grave symptoms, necessitating extensive operations.

The etiology of endometriosis, or adenomyosis, has been the subject of much discussion by gynecologists and pathologists, and the probability is, as Ewing has suggested, that similar tumors, included at present under the same name by various authors, have entirely different origins. The various theories as to the origin of these interesting tumors are as follows: (1) They develop in adult life from embryonic rests from Müllerian ducts or the wolffian body. (2) They are diverticula of endometrium, invading the uterine wall or adherent structures. (3) They develop by metastasis through the blood or lymph stream. (4) Metaplasia of the serosal endothelium, into tissue resembling endometrium, takes place as the result of inflammatory reaction. (5) Any of the tissues that have the coelom as a common anlage may revert into tissue resembling endometrium as the result of hormonal influences. (6) Living endometrial tissue is implanted on pelvic peritoneum and the ovaries, as the result of retrograde menstruation through the fallopian tubes. Advancement of this last view, by Sampson, and his suggestion of the name "endometriosis," have been the cause of much discussion and of many papers on the subject by leading gynecologists throughout the civilized world.

It is not my purpose to go into an evaluation of the relative merits of the various theories. However, one point against the theory of reflux of menstrual products, that never has been mentioned, so far as I know, in the extensive literature on the subject, is the fact that instead of the tubes being open, as has been contended by Sampson,[4] it would be expected that they would be closed as the result of adhesions caused by the chemical irritation of the menstrual blood. It is known that in cases of complete obstruction of the uterine cervix, the menstrual fluid accumulates first in the uterine body and then the tubes become dilated. The first blood which comes through the fimbriated end apparently causes dense adhesions at that point. In such cases, gross accumulation of blood is never seen in the culdesac, nor is evidence found that any considerable quantity of blood has ever been there. Instead, a huge hematosalpinx is often found.

Diagnosis.—At present, a preoperative diagnosis of adenomyoma, ectopic

adenomyoma, endometrioma or endometriosis is frequently made. The symptoms, however, vary so much that it is not possible to be correct in a very high percentage of cases. The factors that, if present, will help most in making a correct diagnosis are: (1) a patient's age of between 25 and 45 years; (2) dysmenorrhea of the acquired type; (3) pelvic discomfort, often extending to the sacrum, into the rectum, or down the thighs, always worse at the time of menstruation; (4) menorrhagia; (5) sterility which may be absolute but more often is relative; and (6) dyspareunia. The findings on bimanual pelvic examination vary with any associated pathologic condition that may be present, and with the extent and situation of the disease. A frequent finding is

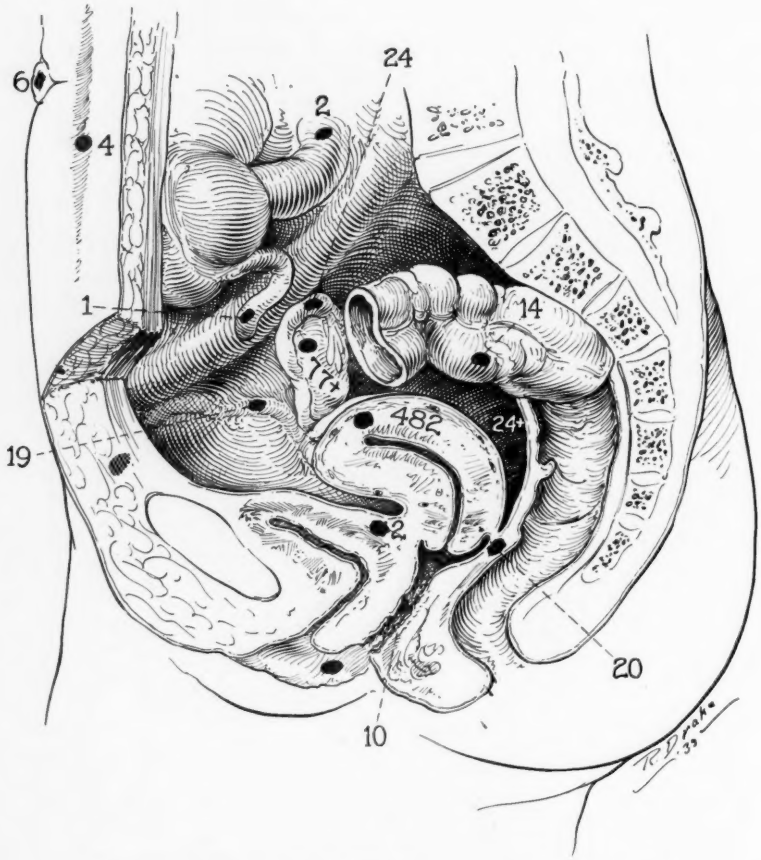

FIG. 1.—Showing situations where adenomyomas have been reported.

adhesions, causing fixed retroversion of the uterus, with or without recognizable tumor; also, thickening in the adnexal regions and tenderness on pressure. In some cases cysts several centimeters in diameter develop in the ovaries. Small, irregular nodules or thickenings of the rectovaginal septum, or in the culdesac, best felt on rectal examination, are highly suggestive.

Incidence.—The incidence of endometriosis is hard to determine, for many

of the tumors are small and are not recognized by many surgeons or pathologists in routine examination of removed tissue.

Situations where heterotopic endometrium or tissue resembling endometrium have been reported to have been found (Fig. 1) are as follows: (1) in the uterus, where the growths may be diffuse or discrete and (2) outside the uterus, where they may be in the ovaries, rectovaginal septum, uterine ligaments, fallopian tubes, abdominal wall, umbilicus, groin, intestinal wall, wall of the bladder, or the vagina (Table I).

TABLE I

Situations of Adenomyomas That Formed the Bases of This Study: Operations Performed in The Mayo Clinic, 1923–1934, Inclusive

Organ*	Number
Uterus	482
Ovary (probably not complete)	77
Rectovaginal septum	20
Ligaments of uterus	19
Sigmoid	14
Pelvic peritoneum	24
Ileum	2
Umbilicus	6
Fallopian tube	22
Vaginal wall	10
Appendix	1
Bladder	2
Abdominal wall	10
Total organs	689
Total patients	576

* More than one organ may be affected. Therefore, the total does not add to 100 per cent.

DIFFUSE ADENOMYOSIS

Relatively frequently, diffuse adenomyosis is found in uteri removed from women who soon will reach the menopause. Many of these patients give histories of having a severe, acquired type of dysmenorrhea, menorrhagia, and sterility of several years' duration; previous to that time they may have borne two or more children. The uterus may be three or four times normal size, and regular in outline unless fibromyomas also are present. If the adenomyomas are not removed before the menopause, they undergo atrophy at that time and, as a rule, cause no symptoms. However, the possibility of malignant change taking place in any endometrium or in tissue resembling endometrium must be kept in mind. Malignancy of the body of the uterus is often suspected in these cases, and it can be ruled out only by diagnostic dilatation and curettage and examination of the tissue by a competent pathologist. There is no doubt that the gross appearance of the mucous membrane removed in some of these cases suggests carcinoma of the body of the uterus. Carcinoma and adenomyosis may both be present in the uterine body, inde-

pendent of one another, and fibroid tumors and adenomyosis are rather frequently found associated in the same uterus.

From 1923 to 1934, inclusive, 4,751 uteri were removed from myoma in The Mayo Clinic. Of this number 482, or 10.1 per cent, were found to contain adenomyomas. This incidence is higher than the 5.7 per cent which Cullen[1] found in his series in 1908, or in the series reported by MacCarty and Blackman[3] in 1918, in which the incidence was 6.43 per cent. In The Mayo Clinic series of 482 cases of adenomyoma of the uterus, it is interesting to note that malignancy was present in 14 cases and that in 280 cases, or 48.8 per cent, some pelvic operation previously had been performed.

Hysterectomy is often advisable in cases of diffuse adenomyosis of the uterus, and because most of the patients are at the age of menopause, or close to it, I believe both ovaries should also be removed. If women are less than 42 years of age, however, and there is no evidence of ectopic adenomyoma, it is advisable to save some ovarian tissue. Radium is being used, I think, too often in these cases, and with rather unsatisfactory results. Cure of symptoms, the most important of which is menorrhagia, will be obtained only if a castrating dose is used, and what is considered a sufficient dose in most cases is often insufficient in cases of marked uterine adenomyosis, probably on account of the thickness of the uterine wall. The beneficial effect, when obtained, is the result of the action on the ovaries, it is not the result of action locally on the growth.

DISCRETE ADENOMYOSIS

"Discrete adenomyosis" is the name applied to a condition in which small circumscribed tumors appear in the uterine wall. This condition is encountered less frequently than is the diffuse form of adenomyosis. The tumors suggest fibromyomas on palpation, but are not encapsulated and have to be cut away from the uterine wall in which they are growing. Their intimate connection with the uterus often suggests a malignant condition. They frequently cause no symptoms. In other cases they cause severe dysmenorrhea and menorrhagia especially if they extend into the cavity of the uterus. They are relatively frequently found in the cornua of the uterus or in the uterine terminations of the fallopian tubes. They do not respond well to radiotherapy, and surgical removal is frequently advisable. Among younger women, myomectomy is advisable but among women who are close to the menopause hysterectomy is justifiable, especially if the tumors are large.

ADENOMYOMAS OF THE ABDOMINAL WALL

Postoperative adenomyomas or endometrial transplants into the abdominal wall are occasionally seen following operations which expose the interior of the uterus. They are seen also sometimes following operations in which the uterus and tubes are not involved. According to Hertzler[2] they occur in about 1 or 2 per cent of cases in which the endometrium has been exposed. In some cases a fistulous tract leads to the uterus. In other cases, a com-

munication with the uterus cannot be demonstrated. The tumor in the abdominal wall, as a rule, appears in a few weeks after the operation but in some cases several years pass before anything abnormal is noted. In some cases the tumors will become larger and painful at each menstrual period and in occasional cases the skin will break over a bluish cystic mass and a small amount of dark fluid will escape. At The Mayo Clinic we have operated in ten cases in the last 11 years. Complete removal of all the adenomyomatous tissue is all that is necessary to effect cure.

ENDOMETRIAL TUMORS OF THE RECTOVAGINAL SEPTUM

Tumors of the rectovaginal septum are the most difficult to treat satisfactorily. As a rule, they cause considerable pain, especially at defecation and at the menses. As a result, they come under observation when they are in an early stage. If neglected, they may grow to considerable size, invading the rectal wall sufficiently to cause obstruction, and occasionally they may ulcerate through the mucosa of the bowel. In other cases, and these are more frequent, the tumors invade the vagina, and a blue-domed cyst, or a polypoid mass of uterine mucosa, may be noted in the posterior fornix; this mass bleeds at the time of menstruation. In still other cases the tumors will grow into the bases of the broad ligaments, may obstruct the ureters, or may cause severe back pain that extends down the legs as the result of pressure on the nerves. If these tumors are seen early, frequently they can be removed by vagina, but if the tumor involves the intestinal wall, resection of part of the anterior rectal wall, hysterectomy, and amputation of the vault of the vagina may be necessary to effect removal. This is seldom justifiable now, even if patients are young. A much simpler and safer procedure is to remove the ovaries or to effect complete castration by radium or roentgen rays. Local treatment of the growth is not necessary. The tumors readily can be distinguished from malignant growths because only in neglected cases of endometrial tumor of the rectovaginal septum is the mucous membrane of the bowel involved. Moreover, differential diagnosis can be made by microscopic examination of tissue. From 1923 to 1934, inclusive, 20 of these tumors were found at The Mayo Clinic.

INVOLVEMENT OF OTHER STRUCTURES

Many of the endometrial growths on the external surface of the fallopian tubes, uterus, uterine ligaments, ovaries, bowel (Fig. 2), and in the culdesac, are small, reddish-brown or purple lesions which bring to mind Sampson's implantation theory, for they are attached only to the peritoneum.

The Ovaries.—Besides the small lesions just mentioned, referred to as implants, cysts several centimeters in diameter are frequently found in the ovary, and from their appearance and situation suggest that they may have started deep in the ovarian tissue. The older and larger cysts are, as a rule, almost black, and cysts of more recent development, containing less blood, are lighter in color. The content of the cysts is apparently irritative to the peritoneum,

for dense adhesions always are found walling them in if they have ruptured previous to operation. It is practically impossible to remove such adherent cysts without rupturing them.

All hemorrhagic cysts of the ovaries are not Sampson cysts, or endometrial in origin, but gynecologists who are especially interested in this subject report finding endometrial tissue in many of them.

Although conservative operations are advisable in these cases, secondary

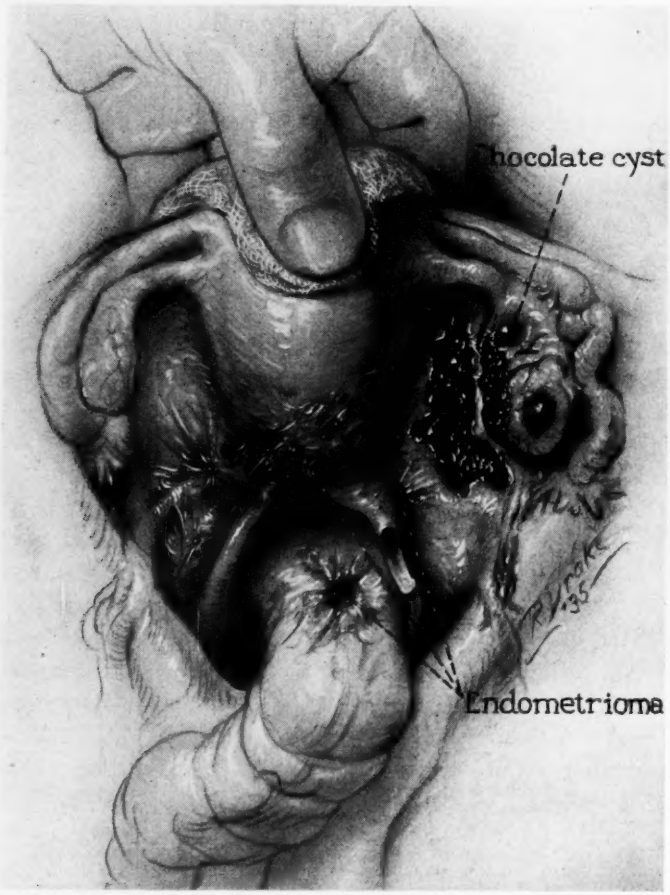

FIG. 2.—Multiple endometrial transplants with endometrioma or adenomyoma in the sigmoidal wall. Small chocolate cysts in the right ovary.

operations are frequently necessary when any ovarian tissue is saved. If it is advisable to remove all ovarian tissue, I believe the uterus should also be removed. The use of roentgen rays and radium is never indicated in these cases. Complications as the result of adhesions make it advisable to remove the pathologic tissues in all these cases. I do not want it inferred that both ovaries should be removed in all cases of hemorrhagic ovarian cyst, but in occasional cases in which there are multiple endometrial implants throughout the pelvis, especially if the rectovaginal septum or bowel is involved, radical

operation is indicated irrespective of the patient's age. Fortunately, most patients who have extensive trouble of this kind involving both ovaries and implants at various other points in the pelvis are very close to the menopause.

The Bowel.—It sometimes happens that growths resembling endometrium develop in the intestinal wall. They are most likely to be confused with malignancy or diverticulitis. In the roentgenogram there will be a filling defect, but there will be nothing distinctive, except in a case of diverticulitis in which multiple diverticula may be visualized at other points in the bowel. If a proctoscope can be inserted up to the region of involvement, change in the mucous membrane will be seen, with ulceration in cases of malignancy, whereas in adenomyoma and diverticulitis there will be no such change. As a further help in diagnosis, adenomyomas are most likely to be found only among women who are between 25 and 45 years of age, whereas diverticulitis and malignant growths are found most often among elderly men. In cases of adenomyoma involving the sigmoid, the patients complain of dull abdominal pain, as a rule associated with constipation which has been progressive over several months or even two or three years. The symptoms are most marked at the time of menstruation and attempts at defecation at this time often bring on rectal spasm. Cachexia is not a symptom in these cases.

On exploring the involved bowel, the external appearance in many cases suggests malignancy, but if adenomyomatous tissue is present at the point of adhesions, or on the surface of the bowel, a definite diagnosis can be made. We now know that adenomyomas undergo atrophy, and seldom give rise to any symptoms after cessation of ovarian function, and the simplest and safest way to treat any of these troublesome tumors is to remove all ovarian tissue. If obstruction exists, or is likely to become complete, temporary colostomy, as a preliminary operation, often is a life-saving measure. Seventeen cases in which there has been definite involvement of the intestinal wall (14 of the sigmoid, two of the ileum, and one of the appendix) have been seen in The Mayo Clinic in the past 11 years.

The Bladder.—The symptoms of an adenomyoma involving the bladder are vesical irritability, increased frequency of urination most marked at the time of menstruation, and hematuria; the blood in the urine may be only microscopic in amount, and blood may be present only during menses. If the tumor involves the base of the bladder, and if one or both ureters are obstructed, renal symptoms are added to the dysuria and hematuria.

On cystoscopic examination the picture naturally will vary with the extent of the lesion, and if tissue resembling endometrium is protruding, polyp-like, into the cavity of the bladder, malignancy will be suspected unless tissue is obtained for diagnosis. At an earlier stage bluish cysts will be visible through the thinned-out vesical mucosa. The bladder wall was involved in two cases in this series.

Treatment naturally varies with the extent and situation of the disease, and also with the age of the patient. Excision is advisable in all cases in which patients constitute good surgical risks, and when it is possible to remove the

tumor without traumatizing the ureters. In the latter type of case, removal of all ovarian tissue will cause rapid atrophy of the tumor. A similar result can be obtained by irradiation sufficient to cause castration. Two cases of adenomyomas of the bladder have been seen at The Mayo Clinic in the last eleven years.

The Umbilicus.—A true umbilical adenomyoma becomes larger and more painful at the time of menstruation, and frequently discharges a small amount of dark bloody fluid at that time. It is difficult to explain the genesis of this type of tumor in the region of the umbilicus except as metaplasia of the peritoneum. Surgical removal of the tumor and the umbilicus, and an overlapping type of closure, are advisable in all cases. In the last 11 years, six patients who had adenomyoma of the umbilicus have been operated on at The Mayo Clinic.

SUMMARY AND CONCLUSIONS

The genesis of adenomyoma is still an unsettled question. Probably some tumors containing tissues resembling the endometrium are in no way related to the Müllerian ducts.

Adenomyomas are of special interest because they represent a non-malignant invasion of normal tissue and such a condition is not recognized by pathologists as occurring anywhere else in the body.

It is recognized that many adenomyomas are found accidentally at operation and apparently do not cause symptoms. In other cases they may cause symptoms or may endanger the life of the patient.

In some cases removal of the tumor is indicated, but in other cases bilateral oophorectomy, use of radium or roentgen rays is a safer and quite as satisfactory a method of controlling the condition.

In the past 11 years a diagnosis of adenomyoma has been made 681 times from tissue removed from 574 patients at The Mayo Clinic.

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DISCUSSION.—HENRY T. HUTCHINS, M.D. (Boston, Mass).—Many strange pathologic conditions are present in the human body which still await an adequate explanation. It would seem that perhaps these occur more frequently in the female than in the male. Not the least of them, and one of the most interesting from a surgical standpoint, is the condition under discussion, which we call endometriosis—in other words, a hyperplasia of endometrial-like tissue in parts of the abdomen and pelvis where we have no reason to

expect endometrial tissue to be present. How this tissue is transplanted does not form a part of this discussion, but what symptoms it causes and what can be done surgically to relieve these symptoms constitute the situation with which surgeons are confronted.

As Doctor Masson has so well expressed it, these lesions represent a nonmalignant invasion of normal tissue, a condition not recognized anywhere else in the body. It is probable that the attention of gynecologists has been more forcibly called to this condition than has that of the general surgeon, because we are operating constantly in the field where these tumors and implantations occur. I want first to call attention to the early recognition of these tumors in order that more conservative treatment may be carried out. As seen in the pelvis, and I am speaking now only of the endometrial peritoneal implants and not of the uterine adenomyomas, we see first only a small black dot often the size of the head of a pin and resembling a small petechial hemorrhage. This is the telltale lesion which is so frequently overlooked. It may be found anywhere in the lower abdominal cavity, on the appendix, on the ileum, on the sigmoid, and of course on the prevesical peritoneum and in the culdesac. This tiny lesion antedates the later adherent stage which is more easily recognized. Although only one of these black spots is seen, both ovaries and the entire pelvis must be searched for the initial endometrioma. When recognized in this early stage, I believe that in the young woman under 35 years we may be conservative in our treatment. The chances are that the initial lesion will be found in one ovary only. It is my practice in these early cases to remove only the ovary which is diseased. Following this conservative treatment many pregnancies have resulted, and the normal ovarian functions will be retained. The patient should, however, be kept under observation for a period of at least five years in order that we may detect the onset of any invasions of a recurrent lesion—invasions especially of the rectum, rectovaginal septum and bladder. In patients over 35 years of age, all ovarian tissue should be removed for it is known that the ovary furnishes the stimulus to the growth of these implants, and no matter how extensive they may be, the tissue will retrograde if all ovarian substance is removed.

The surgical complications of this disease are almost always caused by the invasion of normal tissue by a definite growth, and by far the most serious, as I have seen it, is the invasion of the wall of the rectum causing an increasing constipation due to a gradual stenosis. I have several times mistaken these growths for carcinoma both after roentgenologic examination and also after having opened the abdomen. The recognition of the lesion in the ovary has so far saved me from any resections of the sigmoid or rectum, even with a maximum degree of obstruction. These patients have all recovered and the bowel has returned to normal following complete removal of ovarian tissue.

It is probable that some cases of endometrial implants become in time carcinomatous, but I do not feel that this is fully proven at present. Cases have been reported of associated carcinoma, especially of the rectum, but we have no positive pathologic evidence that the carcinoma originated in the endometrial implant. I have not had a case that has developed carcinoma following an operation for endometriosis although I have seen associated cases.

This disease, as Doctor Masson has so clearly brought out, is difficult to diagnose before operation—in fact, in the early stages it is impossible. When once the lower abdomen is opened, however, it is well, before inserting the hand, to inspect the peritoneum carefully for the small black superficial dots which will lead one to suspect the condition. The treatment will then become conservative in the younger and radical in the older patients. The worst that

can happen to the younger patients is a later operation for removal of the other ovary, and the older patients will be permanently cured.

I agree with Doctor Masson that deep roentgen ray therapy should not be used in these patients. In the young, large sterilizing doses must be given, following which the patient cannot become pregnant, if this is desirable, and in the extensive adherent lesions a real pelvic peritonitis can be induced.

I believe it is important when performing any operation in the lower abdomen and pelvis to search for and recognize these small telltale bluish-black spots on the peritoneal surfaces so that there shall be no possibility of overlooking an early endometriosis with its consequent serious involvement of the bowel, bladder, and rectovaginal septum.

Doctor Gatewood (Chicago, Ill.).—Once in every so often gynecologists seem to discover something new and proceed to confuse the minds of their less imaginative colleagues, the general surgeons, with their discussions. Some years ago, it was ovariotomy, then retroversion, and later vaginal versus abdominal hysterectomy. Recently, it is endometriosis, endometrioma, heterotopic endometrial tissue, adenomyosis, *etc.* This condition may have been recognized before Babes described it in 1882, but it certainly made no great impression on surgeons until Sampson's rather startling observations in 1921 and 1922, in which he demonstrated the frequency of this condition. Since then innumerable articles have appeared championing the transplant theory of Sampson, the wolffian remnant theory, the Müllerian theory, or that of some type of serosal heterotopy. There are many arguments against the theory that implantation of dying desquamated epithelium will grow and produce mesothelial as well as epithelial cells. To these Doctor Masson has added still another good argument. The theory that the tissues of the coelomic cavity may revert to endometrium-like tissue fails to explain why such tumors never occur above the level of the navel. It is also difficult to explain those cases of adenomyosis in the umbilicus itself which are entirely extraperitoneal. Although endometriosis has been seen most often in or on the pelvic peritoneum, it is frequently found also in the uterus itself, in the ovary, in the wall of the cecum and sigmoid, on the bladder and in the umbilicus.

In 1932, Spitz collected 54 cases of umbilical endometriosis and since then several cases have been added, bringing the total up to nearly 70 with the six cases reported by Doctor Masson. To these I would like to add two cases which I have seen at the Presbyterian Hospital.

Case Reports

Case I.—(Presbyterian Hospital Case 303993.) A Mexican female, 43 years old, entered the hospital March 29, 1935, with the following complaints: mass at the umbilicus which had been present for about five years; swelling of the tumor mass at menstruation; pain, developing one day before menstruation and lasting throughout the period; discharge of dark bloody exudate from the umbilicus with each period. The past history was essentially negative. The patient had been married 18 years. She had had two children and one miscarriage. Her menses began at 15 and were regular.

On examination, the umbilical region was a dark bluish color with a nodular mass about the size of a pea protruding from the upper half (Fig. 3). There was a firm ovoid area about three cm. in its transverse diameter in the region of the umbilicus. The margins of this mass were rather indefinite. At operation, an elliptical incision was made about the umbilical region and the entire indurated area was excised. The incision was carried downward in the midline so that the pelvis could be explored. No evidence of endometrial transplants were found on the uterus or on the pelvic peritoneum. The abdominal wound was closed in the usual way except that the fascia was overlapped in the region of the umbilicus. On examination of the specimen the peritoneal surface

was smooth and glistening, and on cut section there was no evidence of attachment of the serosa to the tumor mass. The mass itself was firm in consistency, contained many bluish and brown cysts varying from one to five Mm. in diameter. Microscopic sections (Fig. 4) show the typical arrangement of stroma about tubules lined with columnar epithelial cells which is characteristic of the picture of endometrioma or adenomyosis.

CASE II.—(Presbyterian Hospital Case 289250.) A Polish woman, aged 44, entered the hospital November 23, 1933, on the service of Dr. Carl B. Davis. She complained of a small tumor of the navel which had been present for one year and which had bled at the time of her periods. She stated that something like a tablespoon of blood was discharged at each menstrual period. Except for pneumonia in 1923, her past history was negative. Menstruation began when she was 15 years old and was regular and of the 28-day type. The patient had one child, 23 years old. On examination, there was a firm, purplish mass about 1 cm. in diameter in the lower half of the umbilicus. This was covered with epithelium and not discharging at the time of examination.

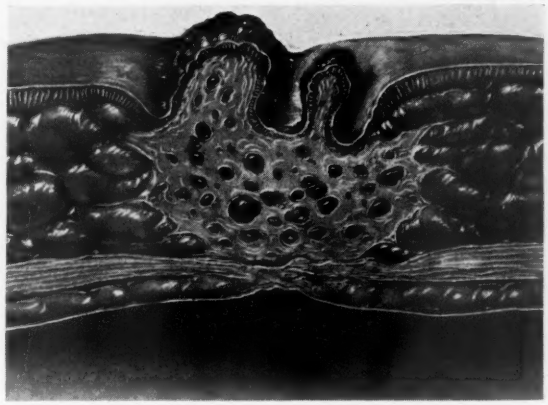

FIG. 3.—Drawing of longitudinal section of endometrioma of umbilicus, showing cystic formation (Presbyterian Hospital Case 303993).

At operation a transverse elliptical incision was made, excising the umbilicus and the tumor mass. A small umbilical hernia containing some omentum was also present. The defect was closed by the Mayo method of imbrication.

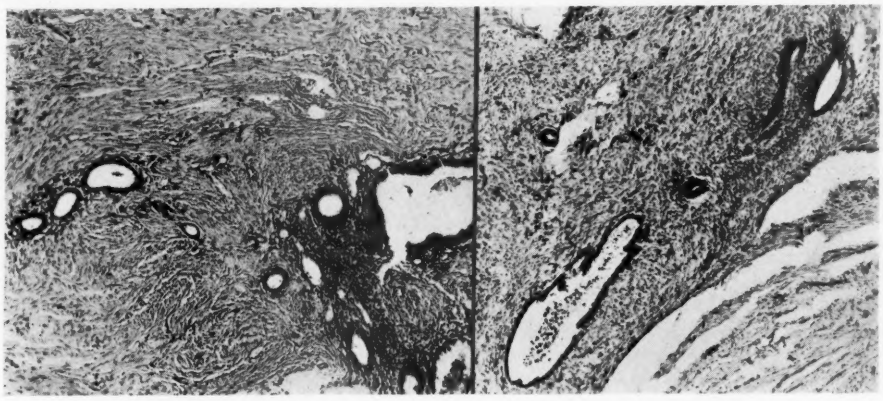

FIG. 4.—Microscopic section of specimen removed from Case I, showing typical arrangement of stroma about tubules lined with columnar epithelium.

FIG. 5.—Microscopic section from Case II, showing desquamation of cells in lumen of a tubule. Note typical arrangement of stroma.

Examination of the specimen showed a smooth peritoneal surface. On section, a firm mass containing small dark colored cysts was found. Microscopic section showed typical endometrial tissue (Fig. 5).

Far be it from me, a mere general surgeon, to enter into the gynecologic dispute as to the etiology of endometriosis. It is quite probable that no single theory can be made to fit all cases, although I should like to suggest a pos-

sibility which would explain the umbilical tumors as well as those within the abdominal cavity. Dr. John Beard, in an excellent series of articles published in the Journal of Anatomy and Physiology, in 1904, entitled "The Germ Cells," maintains that in the skate—and probably also in man—the germinal epithelium does not come from the genital ridge as taught by Waldeyer, and as usually accepted by advocates of the serosal heterotopic theory, but develops in the segmentation cavity of the future embryo and subsequently wanders into it. A considerable number of these germinal cells have been shown to never reach their proper destination in the germinal ridge and may be found without as well as within the abdominal cavity. This view will explain the origin of some of the peculiarly situated dermoid tumors as well as these cases of adenomyosis or endometriosis.

Dr. Edmund Andrews (Chicago, Ill.).—I should like to say a word about a series of four cases of endometriosis with which we have had to deal, three of which were situated in the abdominal wall. It is interesting that all three of the cases with abdominal wall growth were referred to the hospital with the diagnosis of an incarcerated hernia. One of them, however, was seen at the time of the menstrual period and the diagnosis was perfectly obvious. The second case was also diagnosed, but the third was not.

One of the points I should like to ask Doctor Masson is the choice of the time of operation for these cases. One case had the endometrial implant in the umbilical region, and was accompanied by a hernia. The hernia was not diagnosed. We thought it was simply endometriosis. Another case was in the inguinal region. It was small, gave a clear-cut history that was recognized at once. It was seen about two weeks after first examination during menstruation, and obviously smaller and not particularly painful. The woman had been sent in with the diagnosis of hernia. We assured her it was not hernia, and if the condition did not spread or get any worse, operation was advised against. We have not seen her since. That was two years ago.

I should like to ask Doctor Masson—the indications in the other two cases—the first case was an implant in the rectus muscle and it was near, but not in the scar of a previous laparotomy. We operated at the time when the hemorrhage and menstrual reaction was at its height. We then appreciated that it would have been better to have deferred the operation until later. Therefore, the second case was operated on during the intermenstrual period and was very simple, but it left us also with the impression that we had done wrong because it was so difficult to recognize the extent of the endometrial tissue. I think one is between the devil and the deep blue sea, in that the operation at the height of reaction is difficult and bloody, whereas if it is not done at that time, one closes up with the fear he has not excised enough tissue because at the intermenstrual period the tissue is gray, not red. It had not the faintest resemblance to that which we had removed before, and it would be only under the microscope that we could be sure it was endometrial tissue.

Dr. Carl Eggers (New York, N. Y.).—I have repeatedly had endometrioma reported on pathologic specimens in which it was not suspected. They were usually associated with tumor formation of the pelvic organs, most often fibro-angiomata, or ovarian cysts. Occasionally I have found them in other parts of the abdomen including the appendix. I have learned to recognize these tumors by their appearance. They are small, hard, ulcerating-looking-like lesions dark red or bluish-black in color, which cause marked puckering of the surrounding peritoneum, and suggest epithelioma.

It is largely because of the simulation of malignancy that they become surgically of interest and importance.

Case Reports

Case I.—My first experience with such a lesion was in 1929, when, after performing an hysterectomy for fibroid uterus in an unmarried woman, F. H., 43 years old, I noticed a tumor of the sigmoid. The outer end of the left tube was adherent to it. After separating it the tumor was found to be very hard and looked like a typical scirrhus carcinoma. There was no enlargement of the mesenteric lymph nodes. About three inches of the sigmoid were resected and an end-to-end anastomosis done.

After opening the resected portion of gut it was found that the mucous membrane was not involved. The tumor was reported as endometrioma which had invaded the wall of the sigmoid to the submucosa. The convalescence was uneventful. There has been no trouble since.

Case II.—Later that same year, 1929, another patient with an endometrioma was operated upon by me, who had a very interesting history. Mrs. C. T., 37 years old, a married woman, had been under observation and treatment from time to time for six years. In June, 1923, I had operated upon her for an intracanalicular fibroma of the left breast. In October of the same year she had a curettage done, together with a right salpingo-oophorectomy, a left partial oophorectomy and ventrosuspension. The pathologic diagnosis was multiple cysts of follicular origin with hemorrhage. She was much improved after that except for some pain in the left lower abdomen apparently due to disease of the remaining portion of the left ovary.

In 1926 she had first begun to complain of having blood and mucus in the stool, associated with diarrhea. At that time pelvic examination showed a normal sized uterus in good position. A small tender mass was palpable in the culdesac behind the cervix. Abdominal and digital rectal examination were negative. Proctoscopic examination and a barium clysma showed nothing abnormal. A diagnosis of colitis was made. During the next few years she placed herself under the care of different medical men and gastro-enterologists. Her symptoms continued, she became discouraged, lost weight and strength and became quite anemic with hemoglobin of 58 per cent and red blood corpuscles of 3,600,000. Repeated proctoscopic examinations had been reported negative. On several occasions she had been confined to bed and had been given rectal instillations and other treatment. She had noticed repeatedly that the attacks were worse just before and during her menstrual period, but no special significance had been attached to this. She was eventually told that her loss of blood was due to hemorrhoids and that an operation was indicated. It was at this time she again came under my observation. Her chief complaints were pain over the left lower abdomen, attacks of bloody diarrhea and loss of weight and strength.

General examination as well as examination of her blood showed no evidence of constitutional disease. The general abdomen was not distended, but an elevation was noticed over the left lower quadrant, which on palpation felt like a rounded, non-tender mass, apparently arising from the pelvis. Vaginal examination showed the uterus slightly enlarged, and nodular, crowded over towards the right. On the left side a large cystic mass was palpable. A diagnosis of ovarian cyst was made.

Rectal examination was negative. A six inch proctoscope showed nothing abnormal. A longer proctoscope could not be introduced on account of distortion of the sigmoid, apparently the result of pelvic tumor formation. Operation was decided on to remove the pelvic mass and in the hope of finding a condition responsible for the rectal bleeding. It was three years after onset of symptoms connected with the colon and rectum that she was operated upon in July, 1929.

The old median incision was reopened, the omentum was found somewhat adherent to the scar but the loops of small intestines were free. A large cystic mass presented on the left side. It had displaced the sigmoid upward and towards the right. The mass was apparently multilocular. It was very adherent and difficult to liberate. Great

care had to be used not to injure the sigmoid or its vessels. For better access the cyst was punctured with a trocar and considerable clear yellowish fluid evacuated. The mass was then completely freed and removed. It was apparently composed of the ovary and tube. The uterus was nodular, and densely adherent to the anterior surface of the sigmoid. It felt as if one of the fibroids had grown into its wall. It was impossible to free the uterus from above downward posteriorly because of the extensive attachment to the sigmoid. The uterine vessels were therefore ligated on both sides, the cervix was divided and by drawing the uterus upward and backward it could be shelled off the sigmoid and removed. A slit about half an inch in length was noticed in the anterior wall of the sigmoid at the site of attachment. The sigmoid was now completely freed and the injured portion brought into the wound when it was found that it was an upper portion of the sigmoid which had been drawn into the pelvis. Palpation of its lumen revealed a tumor within. The opening into the gut was not sufficiently large to deliver this tumor. It was therefore enlarged and the mass turned out. It was a solid tumor the size of a walnut, which arose from the anterior wall of the sigmoid with a base the size of a dime. The involved portion of gut wall was removed with the tumor. It did not look malignant and impressed us as either a submucous polyp or an endometrial implant. The slit in the sigmoid was closed transversely by means of chromic catgut mucous membrane suture, over which interrupted silk sutures were placed. Some of the appendices epiploica were fastened in place to protect the suture line. Exploration of the sigmoid showed no additional tumors. The cervix canal was cauterized and the stump closed with interrupted chromic catgut. The pelvic floor was peritonealized incompletely. One cigarette drain was passed well down extraperitoneally into the depth of the pelvis and another cigarette drain was placed into the reconstructed culdesac. The abdomen was closed in layers. A transfusion was given immediately after operation.

The convalescence was uneventful. There was no leakage from the intestinal suture line and after the drains were removed the wound healed kindly. There has been no return of symptoms.

Pathologic examination showed multiple fibromyomata of the uterus, multiple cysts of the ovary, chronic salpingo-oophoritis and an endometrial implant with the structure of an adenomyoma involving the wall of the sigmoid and projecting into its lumen like a polypoid tumor.

The following is a description of this tumor.—Section of the separate tumor involving the sigmoid shows it to be an adenomyoma composed of smooth muscle bundles in disorderly arrangement, separated by a considerable amount of fibrous tissue. Scattered through the fibromuscular tumor are large and small endometrial islands or naked uterine glands. The glands vary considerably in size, and some of them have attained cystic proportions. They are regular or sacculated and are lined with a single row of cylindrical cells, some of which show on their free margins structures strongly suggestive of cilia. Some of the islands are very large and contain numerous glandular elements. There are scattered hemorrhages in the supporting cellular stroma and some of the gland tubules contain blood. The growth infiltrates the wall of the sigmoid and in places replaces the muscular coat. The sigmoid mucosa is extremely atrophic in places and shows extensive ulceration. In the better preserved areas it presents enlarged or cystic glands containing numerous goblet cells.

Section through the uterine wall at the attachment of the tumor shows hyperplastic smooth muscle containing a number of scattered endometrial islands similar to those described above, though usually smaller. Some of these are situated on the surface of the roughened area from which the tumor was removed.

Case III.—Mrs. E. N., 44 years old. In 1934 while doing a total hysterectomy for a fibroid uterus, associated with an ulcerated cervix and bilateral ovarian cysts, a small hard tumor was discovered in the sigmoid. It looked like a typical scirrhus carcinoma. After consultation with the family physician immediate resection was decided on, remov-

ing a portion of sigmoid extending one inch above and below the tumor. An end-to-end anastomosis was done.

Upon opening the specimen the mucosa was found to be uninvolved. A frozen section was reported non-malignant. A later pathologic examination showed an endometrioma extending deeply into the muscle layers of the sigmoid. The convalescence was uneventful.

CASE IV.—M. S., 40 years old. In December, 1934, another similar case was operated on by me. The patient was an unmarried woman. She had one large hard fibroid arising from the fundus and reaching to the umbilicus, in addition to several small intramural tumors and bilateral ovarian cysts. The sigmoid was firmly adherent to the mass and a tumor was palpable in its wall. With great care it was possible to separate the gut, which looked puckered and contained a hard flat tumor in its wall. Endometrioma was diagnosed on the gross appearance and the presence of other smaller implants in the pelvic peritoneum. No resection done. Supervaginal hysterectomy with both tubes and ovaries done. Abdomen closed without drainage. Pathologic Report.—Endometrioma of sigmoid.

These cases illustrate the occasional clinical significance of endometrioma and call attention to the importance of being able to make a diagnosis on the gross appearance of the lesions.

DR. JAMES C. MASSON (Rochester, Minn.).—Judging from the numerous articles on endometriosis appearing in the medical literature there is no doubt that the subject is of real interest at the present time. Doctor Eggers' experience, I think, has been most fortunate, but if we could get the complete histories of all patients that have had similar operations (resection of the large bowel for benign tumors), I am sure we would find that a great many deaths occurred from an operation that could have been avoided, if the condition had been recognized before resection was undertaken.

Doctor Andrews' advice to operate in the interval between menstrual periods is sound. There is no doubt that the operation is simpler and safer at such times.

Adenomyomas or endometriomas of the abdominal wall are as a rule small in size and can be easily removed. It is important to keep well away from the growth, in fact taking a little normal tissue along with the tumor. It is possible that some tumors classed as desmoids are true adenomyomas.

In some of these cases I have had to do extensive resection of muscle, leaving a large gap that would predispose to hernia. I think it advisable to take care of the potential hernia at the same time. In these cases the use of living suture, as advised by Doctor Gallie in large herniae, has been a real help.

Doctor Hutchins brings up the question of small lesions so frequently recognized now by gynecologists. There is no doubt that many of them develop into tumors producing symptoms, but it is hard for me to believe that surgical removal is necessary in all cases.

In Sampson's work he reports in all his pelvic work finding about 43 per cent with some involvement. That same large number is reported from Doctor Lynch's Clinic. I have seen these lesions ever since I have been doing surgery. I never used to consider them, in themselves, dangerous unless there was some other definite involvement of the ovary. Most of them do occur where an ovarian cyst has ruptured and scattered endometrium or endometrial-like tissue throughout the pelvis. Sampson considers the ovaries to be like a hot bed for endometrium.

In recent years I have been taking these small lesions off, and it is surprising how frequently endometrium-like tissue is reported in the tissue removed.

OVARIAN TUMORS WITH ENDOCRINE SIGNIFICANCE

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IN THIS day and age discussions of the problems of endocrinology are filling the medical literature to overflowing. Many valuable facts are being added to our knowledge of the normal physiologic behavior of our glands. The pathologic dysfunctions, much more difficult to comprehend, are being slowly worked out step by step. In the study of pathologic conditions of the endocrine glands hyperplasias and tumors are among the most important findings. The understanding of hyperplasias is still in darkness but in some organs tumors having definite functions have been satisfactorily investigated. Such tumors secrete substances that profoundly change the normal individual and their removal is followed by a return to normal. Thus in some tumors the effect of a hormone can be observed and the proof of its potency can be clearly demonstrated.

The ovary is frequently the seat of such physiologic tumors and the recent medical literature contains many reports of such cases. This increased interest in ovarian tumors is due to the emphasis upon hormonology and for the most part our knowledge is directly attributable to the researches and writings of one man, Professor Dr. Robert Meyer,[2, 3, 4, 5, 6, 7] of Berlin. He clarified for all of us the embryology, pathology, and physiology of the arrhenoblastomas, the disgerminomas, the granulosal cell tumors, and others. His observations have led to the frenzied search of old microscopic slides in our Pathology Laboratories. For the next few years all the great laboratories will be presenting reports of cases of odd or interesting ovarian tumors. That these tumors had been misunderstood and misdiagnosed was made clear to us at the Massachusetts General Hospital when seven granulosal cell tumors and five disgerminomas or seminomas were uncovered. These tumors were rediscovered in 1931 and later among a small proportion of all the ovarian tumors in that hospital. At present there is a much more comprehensive review in progress accompanied by a careful follow up of all the patients from whom the tumors were removed. Undoubtedly arrhenoblastomas and testicular adenomas have been overlooked and a careful study should bring more of these interesting growths to light. The presence of postmenopause bleeding and hyperplasia of the endometrium in various types of ovarian neoplasms points to the fact that probably many other types of growths secrete the female sex hormone or an allied substance.

It is the purpose of this paper to describe briefly the interesting characteristics of the now known group of physiologic neoplasms of the ovary and to

report in greater detail some of the characteristics of the disgerminomas and granulosal cell tumors found in our laboratory. In Table I are presented the now known types of ovarian tumors with definite endocrine significance.

TABLE I

Ovario-testis
Testicular tubular adenoma of Pick
Arrhenoblastoma
Hypernephroma of adrenal origin
Disgerminoma or seminoma
Granulosal cell tumor

The first three probably secrete the male sex hormone in varying degrees, producing hermaphroditism in some instances and masculinization, moderate to severe, in others. The hypernephroma of the ovary, and it must be a hypernephroma of adrenal origin, secretes the adrenal cortex hormone that produces the "infant hercules" in the male and the marked masculinization in the female. Such conditions are seen in true adrenal cortex hyperplasia, adenoma, and carcinoma. The disgerminoma or seminoma does not cause masculinization but in some manner retards normal development and is responsible for female hypoplasia. Considering the disgerminoma as a teratoma or twin of the host the maldevelopment of the latter might be explained as that usual in the "free martin" (the undeveloped female twin of a well developed male). The granulosal cell tumor is the only femininizing tumor in this ovarian series and it secretes the hormone estrin or theelin. Thus it is evident that most of these interesting lesions are male directed. The male is dominant in the human and female attributes are possible only through lack of male domination. In the male femininization is rarely seen. Gynecomastia has been reported in males with teratomas containing chorionic tissue. The absence of the male hormone only brings about a neutral state, while in the female removal of the female hormone even without the presence of any male hormone frequently changes the castrate toward the masculine side, for example the growth of hair, change of voice and fat distribution, and the hypertrophied clitoris of the menopause.

The testicle, the adrenal, and the ovary all originate together in one small area in the celomic epithelium and the testicle and ovary have a common ancestor in the embryonal inner and outer epithelial cell masses. The epoophoron and the epididymis are homologues as are the paroophoron and the paradidymis, just as the rete ovarii is the counterpart in the ovary of the rete testis. With such a similar origin it is not difficult to understand how undifferentiated, indifferent, or even primitive male directed cells can be imprisoned in the ovary only to develop later at an opportune time. The origin of the cells of the granulosal cell tumor is in much greater dispute but the primitive cells that make up the original cells of the graafian follicle are probably responsible. That the granulosal cells of the adult follicle are responsible is somewhat questionable. In this hot bed of embryologic remains it does not seem unreasonable to assume that primitive testicular or primitive

ovarian cells may be preserved until some stimulation causes them to grow and produce their hormone.

THE TUMORS

The ovario-testis is a benign lesion. It is an embryonal abnormality and probably not a true tumor. Its origin is attributed to normal testicular cells

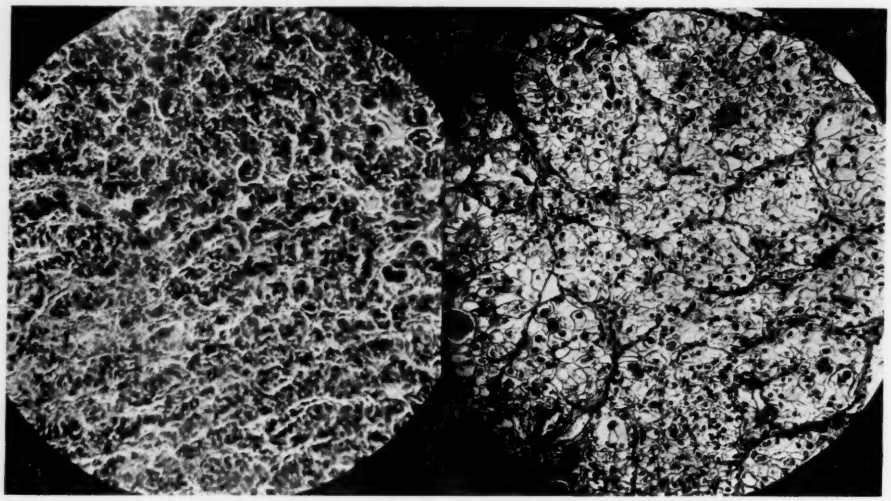

FIG. 1. FIG. 2.

FIG. 1.—Arrhenoblastoma. Photomicrograph of a slide given the author by Prof. Dr. Robert Meyer. Short epithelial cords with a rather characteristic appearance. Numerous dilated endothelial centers are frequently seen.

FIG. 2.—Tumor of the ovary suggesting hypernephroma or a tumor of renal origin. Such a tumor with masculinization of the patient would suggest a suprarenal lesion.

persisting in a developing ovary. A fairly true testicle is formed which is dominant over the weakened ovary. This monstrosity may be responsible for hermaphroditism and masculinization and its removal, if all testicular parts can be excised, returns the patient to normal, provided the anatomic development of a hypo- or epispadias has not progressed too far.

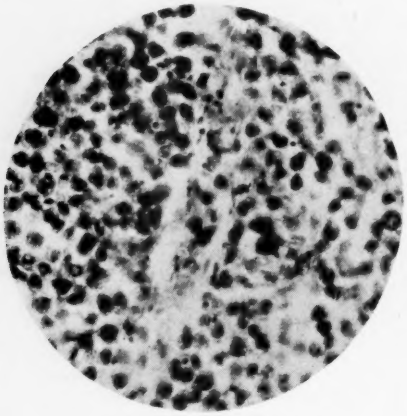

FIG. 3.—Photomicrograph of a disgerminoma. The nuclei are large, and mitotic figures are not infrequent. There is usually a stroma of connective tissue containing many lymphocytes between the groups of cells.

The testicular tubular adenoma was first described by Ludwig Pick in 1905. In this tumor there is an adenomatous development in the testicular portion of the ovary. Frequently this occurs in the ovario-testis but it may be present in lesions not of the ovario-testis type. Microscopically this tumor cannot be distinguished from the testicular tubular adenoma of the testicle. This adenoma, classified as one type of arrhenoblastoma

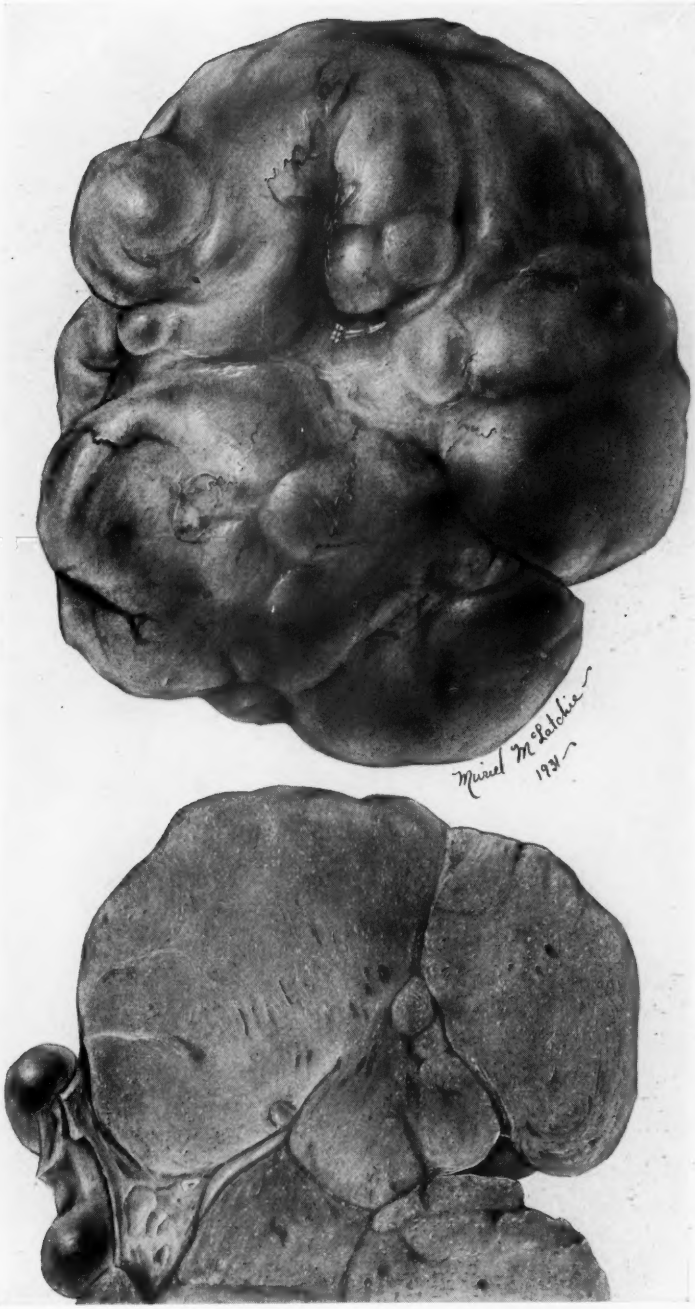

FIG. 4.—Disgerminoma, a solid, smooth, lobulated tumor. Its appearance is characteristic of a very malignant lesion.

by Meyer, is the least masculinizing of the group. The more differentiated toward the normal the arrhenoblastoma is the less masculine the victim. On removal of such an adenoma the patient becomes refeminized if only one small ovule is left in the remaining ovary.

The arrhenoblastomata are of different types. They arise from the undif-

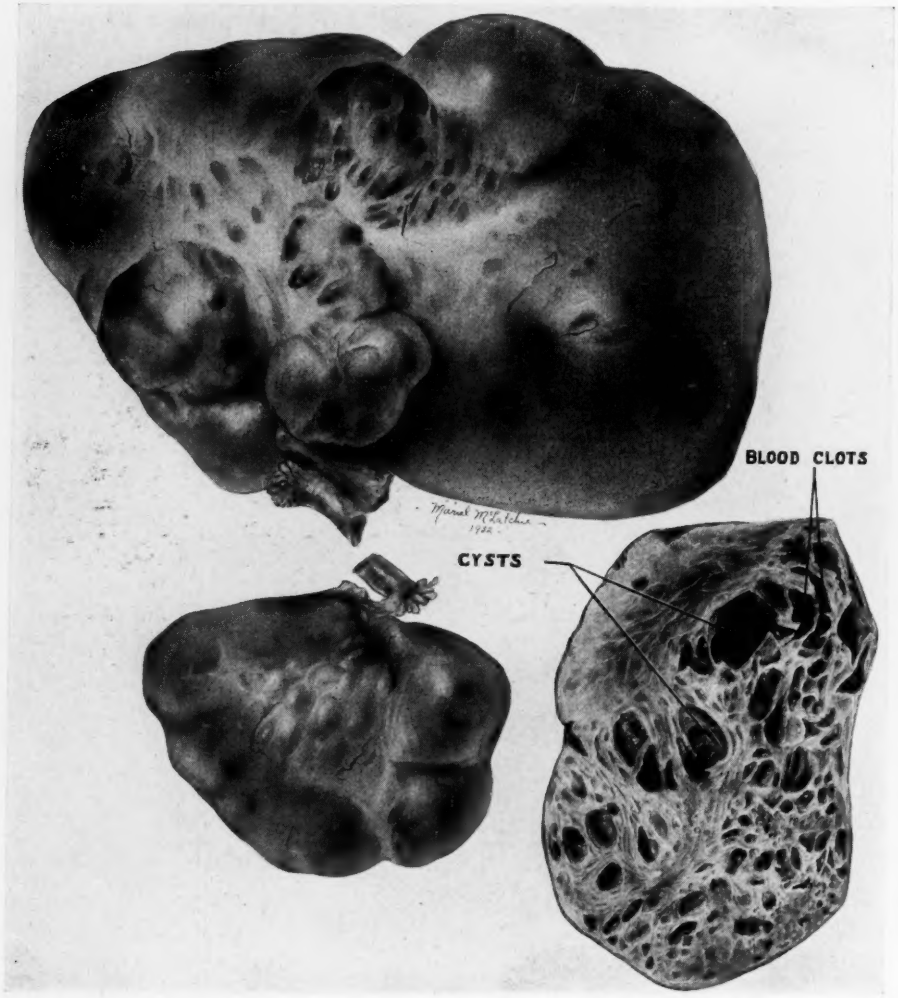

FIG. 5.—Granulosal cell tumor, a solid and cystic lesion of smooth, lobulated appearance. Usually unilateral.

ferentiated germ cells or indifferent sex cells and produce a semi-malignant or very malignant semi-solid or cystic tumor. The complexity of the pathologic picture (Fig. 1) is great but short wavy epithelial cords plus dilated endothelial cavities are characteristic. The tumor secretes an abundance of the male hormone and is responsible for considerable masculinization. The patient loses her scalp hair; grows hair on the shoulders, upper arms, and thighs; the breasts atrophy; and the bony framework of the body suggests the masculine. The abdominal hair has a masculine distribution, striae

are present, the clitoris enlarges, amenorrhea develops, and the voice changes. Removal of such a tumor allows the patient to revert to normal, all except the voice change, which may be permanent. Such a tumor may recur and in so doing the patient again becomes masculine in type.

Hypernephromas of the adrenal type in the ovary are rare lesions and but few of the reported ones have been authenticated. These lesions, secreting as they do the same hormone as the adrenal cortex, hyperplasias and tumors, produce a masculinization similar to that of the arrhenoblastoma. The tumor is regarded as malignant and its removal allows femininization to develop. One slide (Fig. 2) in our series was very suggestive of this type of lesion but it is possible that the tumor was of the kidney hypernephroma type as no masculinization was evident in the patient.

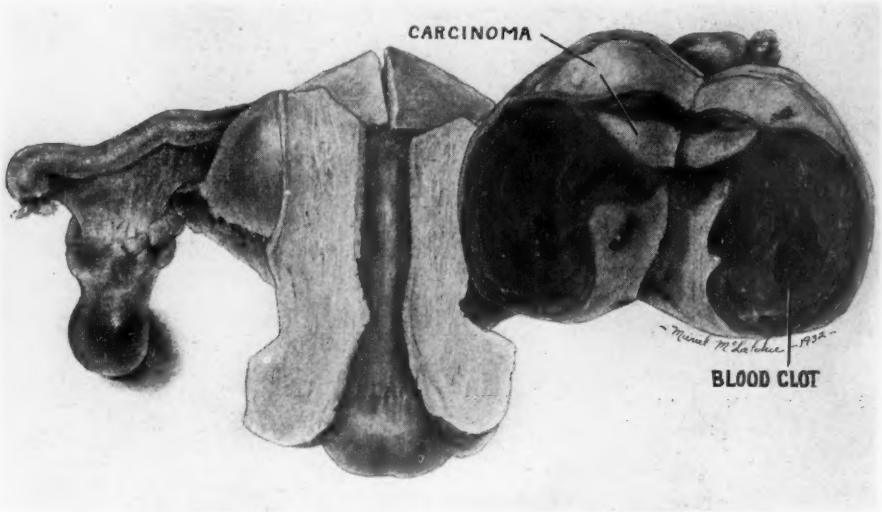

FIG. 6.—Granulosal cell tumor, a smooth tumor about 6.5 cm. in diameter. There is a light solid area of tumor and the dark areas are blood clot.

The disgerminoma or seminoma is a tumor originating in the indifferent sex cells of the ovary. This is a tumor of youth and its hormone is potent enough to prevent proper female development in some cases and disturbances of the menses in others. It is a large round cell carcinoma with large nuclei and the stroma between masses of these large cells is full of lymphocytes (Fig. 3). The microscopic picture is characteristic. This tumor which looks very malignant (Fig. 4), as do all solid carcinomas of youth, is apparently not severely so, as of five cases that have come to our attention four are alive and well over four years. In one of our cases the tumor was responsible for a serious under development of the patient. The other ovary was minute, the uterus infantile, and the breasts under developed. Both ovaries were removed at the operation so it can never be known whether or not the patient would have developed properly once the tumor was removed. One other of our patients who had a menstrual dysfunction when the disgerminoma was present gave birth to a child seven years after her operation.

FIG. 7.

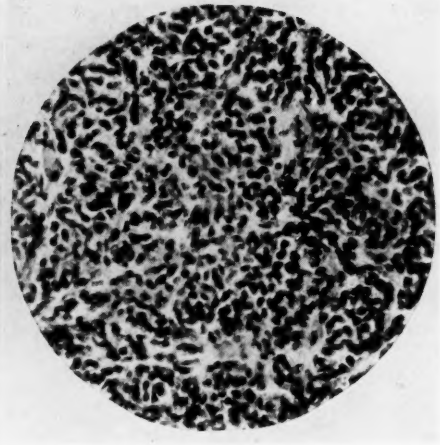

FIG. 8.

FIG. 7.—Photomicrograph of a granulosal cell tumor—low power. The cells are like the granulosal cells of the graafian follicle. Attempts to create active follicular structures are plainly seen.
FIG. 8.—Photomicrograph of a granulosal cell tumor—high power. The cells are very regular and of about the same size. Their resemblance to granulosal cells is very striking.

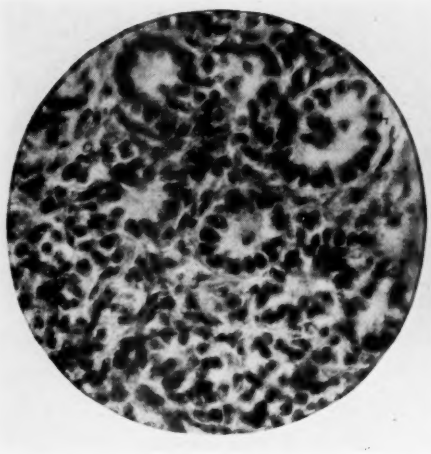

FIG. 9.

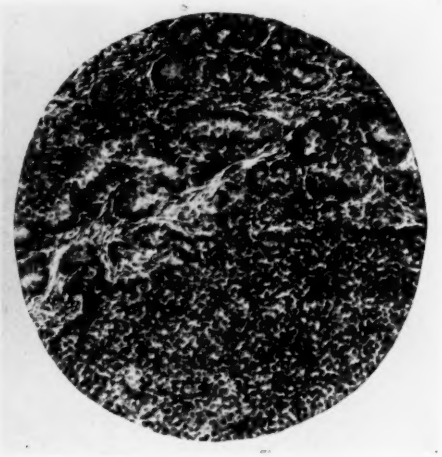

FIG. 10.

FIG. 9.—Photomicrograph of a granulosal cell tumor—high power. Here the attempt to create follicles is evident.
FIG. 10.—Photomicrograph of a granulosal cell tumor—low power. The tubular type of tumor. Notice the regularity of the cells in the lower part of reproduction. These have the appearance of typical granulosal cells.

TABLE II

Disgerminoma—Seminoma

5 cases—25, 23 (2), 18, 12
Undeveloped genitalia..... 1
Abnormal catamenia..... 3
Living 9 yrs., 8 yrs., 7 yrs., 4 yrs.
Dead 1—extensive at time of operation.

The granulosal cell tumor (Figs. 5 and 6) is both benign and malignant. It originates from the follicular apparatus whether primitive or adult. The cells lining the graafian follicle are granulosal cells and the tumor closely resembles masses of these cells. Although it grows in tubular, sarcomatous, and follicular type it is usually easy to diagnose microscopically (Figs. 7, 8, 9, and 10). They were incorrectly called sarcomas or embryonal carcinomas in the first laboratory study. Tumors of this type are responsible for precocious femininity and early menstruation in young girls and such children

FIG. 11.—Photomicrograph of the endometrium in a case of granulosal cell tumor. Hyperplasia of the swiss cheese type is clearly shown.

should be considered as possible hosts of the lesion. Removal of the tumor checks the femininization and the child reverts to normal. In adults this lesion is responsible for abnormal bleeding of the estrin type with hyperplasia of the endometrium (Fig. 11). Removal of the tumor corrects the abnormal menstrual flow. In older women past the menopause they cause hyper-femininization as evidenced by menstruation of the non-ovulatory type occurring either as continuous, irregular, or periodic bleeding. Removal of the lesion stops the abnormal flow. In any patient in adult life and especially in those past the menopause the presence of bleeding and hyperplasia necessitates a careful search for such a tumor. The neoplasms are frequently malignant and radical surgery is perhaps best. Of seven cases seen at the Massachusetts General Hospital all were under 50 years of age and of these two have died of their cancer.

TABLE III

Granulosal Cell Tumor

Ages—26	1	Bilateral	2
33	1	Fibroids	1
36	1	Endometrium examined	2
39	1	Hyperplasia	2
41	2	Solid	3
42	1	Sarcomatous	3
Married	7	Tubular	1
Children	6	Living (2.5 years and 5 years)	2
Menorrhagia	2	Living without disease (7 months and 8 months)	2
Regular periods	3	Lost	1
Brown discharge	1	Dead (1 year and 2 years)	2
Amenorrhea (menopause)	1		

Below in brief outline are presented the histories, physical and pathologic examinations of five cases of disgerminoma or seminomas and seven cases of granulosal cell tumors.

CASE REPORTS

Disgerminoma—Seminoma

Five cases

CASE I.—L. M. C., aged 23. Single. Complaining of diarrhea for two months and pain in the right side. She noticed enlargement of the abdomen eight months before. Her periods began at 13 and had always been regular. She was well developed and nourished with no abnormality of secondary sex characteristics or abnormality of sex feelings. Physical examination showed a large mass in her abdomen. At operation a large ovarian tumor was removed. The tumor measured 21 cm. by 19 cm. There is no record of the gross description of the tumor. The microscopic picture was typical of a disgerminoma or seminoma. This patient was seen and examined in April, 1935, and found to be perfectly normal nine years after the original operation.

CASE II.—H. H. 31:437. L. A., aged 18. Single. Complaining of abdominal swelling with intermittent dull and sharp pain. Her periods began at 13 and gradually assumed a 28 day cycle. Lately she has been flowing four to five days early. The patient was well developed and well nourished. There was a large mass in her lower abdomen. At operation a heavy, knobby tumor, partially twisted, was found filling the lower half of the abdomen. It was removed. The pathologic report showed a tumor of the ovary, 17 cm. by 14 cm. It was lobulated, irregular, and pale pink. On cross section it was a soft cellular new growth with areas of hemorrhage. A diagnosis of embryonal tumor of the ovary (adenocarcinoma type) was made. The slides of this tumor are characteristic of the disgerminoma (seminoma). In May, 1935, four years after the operation, the patient without further treatment is alive and well and normal in appearance without evident disease.

CASE III.—M. G. H. 261448. V. K., aged 12. Single. Complaining of lump in middle of her lower abdomen of one and one-half month's duration. This lump had grown slowly in size. Periods began four months ago and since then the patient has had two periods and skipped two periods; alternating. The patient was a well developed and well nourished girl. Physical examination showed a mass in the pelvis which could not be differentiated from the uterus since the cervix apparently was continuous with the mass or the uterus was adherent to it. At operation a solid, lobulated, vascular tumor springing from the right ovary was found and removed, leaving the right tube. The

pathologic report showed a solid, spherical tumor, the size of a cantaloupe, measuring 9.5 by 14.5 by 16.5 cm. Its surface was smooth and nodular. On section it was moist and grayish-white with small, yellowish, opaque areas. Microscopic examination showed alveolar clusters of large undifferentiated epithelial cells and reactionary stroma. Picture was typical of seminoma or disgerminoma. In February, 1931, seven years following operation, a baby was born to the patient and she was seen eight years following the operation and was feeling very well. Menstruation has been normal since the first month after childbirth.

CASE IV.—M. G. H. 235259. J. W., aged 23. Married. Three children. No miscarriages. Complaining of lump in right side of three years' duration. This grew very slightly but caused her no trouble until three weeks ago when she noticed increased abdominal enlargement at the site of the tumor. There was no pain but the tumor was tender. The patient has been flowing every day for the past two weeks. Periods were regular until eight years ago since which time they have not been so regular. She has slight dysmenorrhea. The patient was poorly developed and very poorly nourished. Physical examination showed a mass easily felt on pelvic examination. There was tenderness on the right side. At operation a large, nodular, hard tumor was found arising from the left ovary and filling the pelvis and lower abdomen. The upper two-thirds of tumor was amputated, and the right ovary which was cystic was removed. The peritoneum was studded with nodules. The liver was free of disease. The pathologic examination showed an irregular solid tumor, measuring 10.5 by 12.5 by 21 cm. with a smaller mass about the size of a small orange, the combined weight of the two being 1,480 Gm. On section it was composed of a homogeneous soft white surface with small areas of opaque yellow softening. Microscopic examination showed solid masses of undifferentiated epithelial cells, among which are groups of small cells, the size of lymphocytes. There is a variable amount of stroma. The slides of this tumor were characteristic of seminoma or disgerminoma. The patient was given five radium treatments over a period of five months. She died one and one-half months following treatment.

CASE V.—M. G. H. 269006. E. C., aged 25. Single. Complaining of pain in the left lower abdomen, "nagging" in character, of two months' duration. Vomiting with last two attacks of pain. Patient had never menstruated. She was well developed and well nourished, of a stolid type. Breasts were not developed and she had sexual infantilism. Physical examination showed a soft, level abdomen with some tenderness in the right and left lower quadrants. Slight rigidity but no spasm. There was a mass three to four cm. in diameter in the region of the left kidney. Genitals were undeveloped for patient's age. On rectal examination she was found to have a small retroverted uterus. At operation a small, diminutive cervix was revealed, into which a small probe passed for a distance of about one to one and one-half inches. Abdominal exploration revealed a pelvis with a diminutive ovary on the right. In the posterior culdesac there was a dark blue solid growth which proved to be a solid tumor of the left ovary, as large as a tennis ball, the pedicle of which was twisted one and one-half times. Both tubes, left ovary and tumor, and what may have been the remnant of ovarian tissue on the right were removed. The pathologic report described a spherical solid tumor with deep purplish-red surface and oviduct attached. On section it was 4 cm. in diameter and showed a soft, dull, purplish-red surface. The other oviduct also had a purplish-red surface. A small yellowish nodule was seen in the broad ligament below it. Microscopic section of ovarian tumor showed a tissue which was largely necrotic and filled with blood and wandering cells. In places alveolar clusters of large atypical epithelial cells, somewhat degenerated, were found. No ovarian substance was identified in the nodule in the broad ligament. The slides were characteristic of disgerminoma. On examination of the patient in April, 1932, seven years after operation she was found to have markedly infantile breasts, small and cone shaped, very sparse hair on the vulva and mons veneris. The labia minora were practically gone. The vagina was extremely infantile and could

be just entered with the finger. The cervix was not felt. On rectal examination nothing was demonstrable in the pelvis. The patient had marked genital and breast infantilism. She wished to be married and was advised to do so providing her husband knew she could not have children. The patient has never menstruated.

Granulosal Cell Tumors

Seven cases

CASE I.—M. G. H. 277980. S. S., aged 41. Married. One child. No miscarriages. Complaining of excessive flowing for four months. Three years ago she had a lump in the lower abdomen and pain which lasted only a short while. Sixteen months ago she was curetted for excessive flowing. She has passed large clots at times. Periods were always irregular with only a small amount of bleeding. Patient was well developed and well nourished. Physical examination showed vaults clear and fundus in anterior position and moderately enlarged. At operation a right ovarian cyst, the size of an orange, was found and ovaries were removed. Pathologic examination showed a cystic tumor 6.5 cm. containing mushy, wet, yellowish material. Microscopic examination showed a richly cellular growth. Cells were not differentiated and were small. The slides were characteristic of granulosa cell carcinoma. Follow up has not been successful.

CASE II.—M. G. H. 185045. N. D., aged 42. Married. Five children. One miscarriage. Complaining of fulness and abdominal distention after meals of two months' duration. Has felt rundown for several months. There has been increase in the size of the abdomen for 11 days. She has had frequency of urination for three months. Abundant flatus. Periods have always been regular. Occasional slight leukorrhea. Patient is well developed and well nourished. Physical examination showed nothing palpable on bimanual examination on account of distention. At operation two apparently malignant cysts of the ovaries the size of melons were found. Cysts and ovaries removed. Peritoneum and liver were covered with many small metastases. The pathologic report showed both ovaries enlarged to the size of an orange, dark red and lobulated. On section there were multiple cysts, some filled with clear fluid and others with solid tissue which had a soft grayish-white surface on section. On microscopic examination of the solid growth there were large masses of epithelial cells separated by a little stroma of connective tissue. Slides were characteristic of granulosal cell carcinoma. The patient died two years following operation.

CASE III.—M. G. H. 237812. A. McK., aged 36. Married. One child. One miscarriage. Complaining of excessive flowing with periods, of 11 months' duration. Slight flowing between periods occasionally. Periods were irregular and slightly painful until operation for removal of cervical polyp eight years ago. Patient was fairly well developed and well nourished. Physical examination showed a rounded tumor in the left culdesac which felt like a cystic ovary or pedunculated fibroid. At operation a right ovarian cyst the size of a base ball was found. Pathologic report described a spherical semisolid tumor the size of a base ball. On section it formed a soft, solid purplish-red mass with one or two small cysts containing clear fluid. On microscopic examination there were solid masses of small undifferentiated epithelial cells in a fibrous stroma with a zone of ovarian tissue on one surface. Picture was typical of granulosal cell carcinoma. The patient was seen two and one-half years after operation and felt very well. No tenderness or masses felt in pelvis. There was a small nodule in the vaginal wall on the right side, the size of a pea; which was not felt to be a recurrence.

CASE IV.—M. G. H. 252102. M. W., aged 39. Married. No children. No miscarriages. Complaining of mass in right lower quadrant for one and one-half years. She believes it is getting progressively larger. Since this time she has noticed vague intestinal symptoms with occasional vomiting. She has urinary frequency—particularly at night. Periods are regular. No dysmenorrhea. Patient is well developed and nourished. Physical examination shows multiple masses palpable bimanually. At opera-

tion the pelvis was full of inflammatory material, the tumor masses were ovarian cysts. Left tumor was of the papillary adenomatous type. The cyst was shelled out of the pelvis and amputated so that a portion of the wall of the cyst was left adherent to the intestine. The left cyst was enucleated by shelling it out transperitoneally. Pathologic examination described a cystic and solid tumor the size of an orange. On section it showed a soft, cystic center and a grayish-white, fleshy cortex. On microscopic examination there were small undifferentiated epithelial cells having an alveolar arrangement, showing numerous mitotic figures. Slides were characteristic of granulosal cell carcinoma with metastases to the oviduct. The patient died one year following operation.

CASE V.—M. G. H. 326234. E. M., aged 26. Married. Three children. One miscarriage. Complaining of dull ache in right lower quadrant of seven years' duration (one month following the birth of the patient's first child). For the past two years the pain has also involved the left lower quadrant; more severe at time of periods. She has also had a foul smelling white to brownish discharge. Legs tire easily. Aggravation of symptoms during and after each labor. Menstrual history not known. The patient was fairly well developed and well nourished. Physical examination showed tenderness in both lower quadrants. There was swelling and tenderness in the region of the right Bartholin's gland. Vaults were free. At operation a Bartholin cyst was excised. A cyst of the right ovary, about 6 cm. in diameter, was found. Right tube and ovary were removed and the uterus suspended. Pathologic report described a cystic ovary measuring 5.5 cm. in diameter. The wall was thin and smooth. On opening it the cyst was filled with serum and lemon jelly-like material. The lining of the cyst was smooth. There was one corpus luteum and a white firm encapsulated tumor one cm. in diameter. On section this mass was firm and finely granular. The microscopic picture was typical of granulosal cell carcinoma. The patient was seen in August, 1933, seven months following operation and was doing well. Her periods were normal. No evidence of disease. No metastasis in vagina. Nothing to suggest recurrence by rectal examination.

CASE VI.—M. G. H. 268025. M. R., aged 33. Married. One child. No miscarriages. Complaining of increase in length of periods for about three years. Amount of flow was not excessive. Nine months ago she flowed steadily for nine weeks. Patient feels well except for weakness. Seven years ago she had a period of amenorrhea lasting for two years but periods then became fairly regular. Patient is well developed and well nourished. Physical examination disclosed a large tumor involving the fundus which was hard, freely movable, and rose nearly to the umbilicus in the left lower quadrant. Behind the cervix the tumor was prominent and had a small prominence on it. This was easily felt by rectum. At operation a solid tumor of the left ovary the size of a baseball was found. The right ovary showed no evidence of disease. The left ovarian tumor was first removed and incised for examination. The cut surface suggested malignancy so it was decided to remove the other ovary and do a hysterectomy on account of the excessive bleeding. On pathologic examination one ovary formed a solid tumor about the size of a tennis ball. On section it had a moist, pale yellow, fibrous surface with small cysts. The other ovary was small and showed a fibrous surface on section without evidence of new growth. On microscopic examination of the solid ovarian tumor there was a richly cellular growth composed of small cells with hyperchromatic nuclei which form compact masses with occasional distinct alveolar clusters. In places these cells differentiated into small compact tubercles. A fibrous stroma pervaded the tumor and ran between the cell masses. The slides were characteristic of granulosal cell carcinoma. Five years later a letter was received from the patient stating she was in the best of health.

CASE VII.—M. G. H. 319722. G. B., aged 41. Married. Three children. Ten miscarriages (chiefly stillbirths). Complaining of foul, whitish, vaginal discharge for two years. Also had pain across lower abdomen, and pain in lower back; aggravated just before period. Periods began at 16 and were regular every 28 days, flowing for five days. With no periods for four months she believed she had passed into the menopause.

Patient was fairly well developed and well nourished. On physical examination a cystic non-tender mass 3 cm. was felt in the left vault. In the right vault there was marked thickening but no definite mass. At operation an atrophic right ovary was found and an ovarian cyst of the left ovary 7 cm. in diameter with the omentum adherent on the posterior surface. The pathologic report disclosed one ovary as small and atrophic and containing a thin walled, smooth-lined, purplish colored cyst which had been opened and measured approximately 2 cm. in diameter. The other ovary was large, ovoid with a smooth, glistening, mottled, reddish-gray surface and measured 6.5 by 4 by 5 cm. in size. It was moderately soft in consistency and on section had a large and irregularly shaped area 4.5 by 2.5 by 3 cm. filled with blood clot and surrounded by a thin yellowish-brown corpus luteum 1 by 1 by 0.5 cm. near the upper pole. The remaining portion of the ovary had a very smooth, glistening, whitish lardaceous appearance. Microscopic examination showed the tumor to consist of small oval to spindle shaped cells of very uniform size with a tendency to alveolar arrangement and the formation of long cords or duct-like structures devoid of lumina. The picture was characteristic of granulosal cell carcinoma. The patient was given one series of roentgen ray treatments about eight months following operation. Seven months after operation she began to have bleeding and pain in hips. Roentgenograms were negative for metastatic malignancy.

SUMMARY

Tumors of endocrine significance are not rare and more diligent search should be made for them in the Pathology Departments of our hospitals. That such physiologic tumors secrete definite hormones may be assumed because of the numerous instances of cases that have been returned to normal following removal of the tumor. The ovary is the seat of a great many functioning tumors and it is possible that as we acquire greater understanding more lesions with important bearings upon the bodily habits will be discovered.

NOTE.—The drawings and photomicrographs in this article have been reproduced from the originals used in "Tumors of the Female Pelvic Organs" by Joe Vincent Meigs,[1] published by the Macmillan Company in 1934. The author wishes to thank the publishers for their courtesy.

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DISCUSSION.—DR. JOHN J. MORTON (Rochester, N. Y.).—It has been known for many years that hyperplasias or tumors in certain organs have produced substances characteristic of the tissues involved. The effects on the individuals concerned have varied from such outstanding changes as acromegaly, or increased basal metabolisms, down to scarcely demonstrable action. Some of the neoplasms, for instance, manufacture substances characteristic of the organ from which they are derived but the general effect on the organism is almost negligible. Thus, cancers of the stomach may make hydrochloric acid; bile duct cancers may secrete bile; or bone sarcomas may develop new bone—all of them, even in their metastatic deposits.

The changes brought about by overproduction of some endocrine substances whether formed in hyperplasias or true tumors are discoveries of relatively recent date. The profound disturbances in calcium metabolism of parathyroid origin; the upsets in sugar metabolism from tumors of the islets of the pancreas; the marked blood pressure regulating action of adrenal paragangliomas; and the sex changes associated with other tumors of endocrine origin have attracted investigators in recent years.

A great impetus was given to these studies when biologic tests for minute quantities of the endocrine substances became available. The causes of the changes in the sexual cycle were revealed for the first time and the relationships to changes in the secondary sexual glands were made out. The progress has been so rapid and from so many sources that at present the names used to designate these endocrine substances are many and varied.

There is little doubt that the endocrine substances released into the circulation by most of the tumors of ovarian origin have the power to modify the individual toward manifestation of male somatic characters as Doctor Meigs has pointed out. The granulosa cell tumors, however, may cause enlargement of the uterus, endometrial hyperplasia, and uterine bleeding either in young children or in adults past the menopause—certainly a modification toward femaleness.

This leads us naturally to a biologic consideration of sex determination. The geneticists have told us in the past that sex is determined by the genic composition of the chromosomes at the time of fertilization. This mechanism still seems to hold for certain forms but for the higher vertebrates the sex glands remain in an undifferentiated stage until influenced by hormones. The anterior hypophysis secretes a gonadotrophic factor which has the power to arouse the dormant sex cells toward differentiation either to maleness or femaleness. The male or female sex hormones formed by the differentiated gonads cause the complete differentiation of the secondary sexual apparatus. Thus, when the ovary starts to develop following hypophyseal stimulation, the wolffian ducts drop out and the müllerian ducts hypertrophy to complete the female sexual apparatus. Certainly under conditions of experimentation

with the sex hormones, the primary germ cells of a given embryo can be made to differentiate either toward maleness, femaleness, or both. This would seem to indicate that the primitive sex cords are potentially hermaphroditic in their ability to respond to either sex hormone.

It is now generally accepted by biologists that there is no antagonistic action between the sex hormones. Each sex hormone is regarded as specific for its own differentiated tissues. But in the normal individual one kind of sex hormone dominates and part of the primitive sex cells remain undifferentiated, acting like a rudimentary structure. In the female ovary the medullary portion contains apparently functionless sex cells which persist from the undifferentiated stage. In the testis there is no corresponding remnant of the primitive sex cells. Consequently, the female always has present a structure which under proper stimulation may differentiate toward maleness.

It may be that the explanation of the trend toward maleness exhibited by certain of the ovarian tumors comes about through a certain amount of dedifferentiation of the cells of the ovary which is necessary in order to have a neoplastic growth. It is well known that tumor growth takes place in undifferentiated or in dedifferentiated tissues. Factors which produce differentiation in general tend to restrict growth. The dedifferentiation of the ovary would tend to remove the conditioning sex hormone and to allow the rudimentary sex cords to assume the male type. There is ample experimental evidence to show that if the female conditioning factors are removed at certain stages the undifferentiated sex cords tend toward maleness (twinning in cattle, castration of ovaries in hens, *etc.*).

The sex hormones—oestrogenic substances—have a peculiar significance in that they are closely related chemically and in their biologic behavior to some of the carcinogenic agents which have been isolated from coal tar. And conversely, some of the carcinogenic agents from coal tar have been shown to have oestrogenic powers biologically on test animals.

The effect of oestrogenic substances on the somatic cells if long enough continued may be to produce hypertrophy or neoplastic growth. This has been demonstrated in animal experimentations. The female sex hormones can cause changes in the uterus, vagina, mammary glands, *etc.* The male sex hormone can cause changes in the prostate, and accessory spermatic ducts. The tissue changes produced by the oestrogenic substances in causing neoplasms differ in one important respect from those produced by the carcinogenic substances recovered from coal tar. The oestrogenic substances produce malignant change only in specific tissues; whereas the carcinogenic agents produce changes in any tissue. The time factor necessary for the production of malignant change is common to both oestrogenic and carcinogenic agents.

DR. JOE V. MEIGS (Boston, Mass.).—There is one thing I would like to say. If you consider the disgerminoma or seminoma of the ovary which causes maldevelopment in the female a teratoma, which it is, and if you consider a teratoma as a twin of its host, which it may be; then as the tumor is dominantly male the patient should be a free martin or a neutral, which one patient in our series was.

CHOICE OF METHODS OF DIVERTING THE URINARY STREAM ABOVE THE LEVEL OF THE BLADDER

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IN THE subsequent discussion it will be assumed that for some one of a variety of reasons the bladder has become for practical purposes either worthless, dangerous, or both.

CONDITIONS FOR WHICH DIVERSION MAY BE NECESSARY

1. *Congenital Anomalies.*—In this group the most outstanding is exstrophy of the bladder in regard to which it may be safely asserted that no plastic operation having for its purpose the construction of an anterior vesical wall and the development of a sphincter has proved satisfactory. For this reason diversion of the urinary stream with removal of the exstrophic bladder is universally agreed upon. Closely allied to this condition is the severe grade of epispadias. This may be defined as a situation in which the superior wall of the urethra is missing together with the sphincter mechanism of the bladder neck. It is probably conservative to suggest that in many or most of these cases an attempt should be made to construct a vesical sphincter and a urethra. This can probably be undertaken without serious danger of infection of the upper urinary tract, although this is an ever present possibility as a sequel of operations for reconstruction of the vesical outlet. In a certain proportion of these cases, apparently from the literature in a considerable proportion, plastic operations will fail to give a satisfactorily continent bladder and the condition must then be dealt with as in exstrophy. Third in this group comes a still undefined group of cases in which there is apparently some congenital defect in the nerve mechanism controlling the musculature of the urinary tract. The commonest clinical picture is the association of incomplete retention of urine and a constant large residual urine with dilatation of the ureters and kidney pelves and often extensive damage to the renal parenchyma. This is today commonly detected in childhood as the result of difficulties in urination or when an incurable pyuria leads to further investigation. With this situation is often associated varying degrees of spina bifida, whether of the occult or the sacculated type. In some instances complete incontinence will be found, associated, however, with functional obstruction of the ureters, apparently from lack of contractility of the muscular structures. The diagnosis is not always simple, since a variety of congenital obstructions at the bladder neck, which

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include valves and other congenital deformities, may give rise to a similar clinical picture, but are remediable by correction of the bladder neck obstruction. Only those cases should be regarded as due to anomalies of the nerve supply in which careful study of the bladder neck quite fails to show any of the anomalies above referred to. As these patients have been seen in the past, their outlook was very hopeless, since satisfactory emptying of the urinary tract could not be obtained, and drainage of the bladder commonly is quite impotent to relieve the stasis in kidney and ureter. It has been suggested that operation upon the sympathetic nerve mechanism, possibly upon the presacral nerve, may be of value to some of these patients. In regard to this one can only say that to date few if any thoroughly satisfactory results have been published. Assuming that remedy of the condition cannot be obtained by dealing with lesions of the bladder neck, and further assuming that operation upon the sympathetic mechanism is not thought desirable, the integrity of the kidneys can be preserved—perhaps over a long period of time—by diversion of the urine above the level of the bladder. They, therefore, come into this category.

2. *Injury to Bladder or Ureters.*—A second important, though not very numerous, group is that with injuries of the bladder or ureters. In this group will be found a small number of cases of unusually large vesicovaginal fistulae, often in patients in whom several atttempts at operative cure have failed. When the stage is reached at which there is insufficient tissue with which to construct a satisfactory bladder floor, then diversion of the urinary stream above that level must be entertained.

Injury of one or both ureters occasionally occurs in connection with pelvic operations, most commonly for cancer. In a proportion of these cases it may be possible to immediately suture the divided ureter if the ends can be approximated without tension. In another moiety the ureter can be reimplanted in the bladder, which, under favorable circumstances and with good technic, is preferable to any operation for diversion. Not uncommonly, however, the injury of the ureter may not be detected or the actual solution of its continuity may not occur until some days after operation. At this time suturing of the ureter will be found considerably more difficult, and reimplantation into the bladder not only more difficult, but associated with a not inconsiderable risk from infection due to a secondary operation in a recently traumatized field. In those cases in which reconstruction of the ureter is impossible, and reimplantation cannot be safely undertaken, diversion above the level of the bladder is indicated.

3. *Non-Tuberculous Chronic Cystitis.*—Third is a not large but important group of cases which will be of inflammatory—non-tuberculous—origin. Although these conditions are described by a variety of names, among others the "elusive ulcer," they are, we believe, all cases of extensive chronic interstitial cystitis. In a considerable number of such cases, at least, the cause is obscure, though in some of them they are the direct result of prolonged infection, perhaps associated with prolonged drainage of the bladder. For those

cases in this group in which contraction of the bladder has gone on to such a point that its capacity is very seriously impaired and in which local treatment combined with periodic overdistention fails to relieve, diversion of the urinary stream above the bladder becomes the method of election.

4. *Tuberculosis.*—This group includes cases of tuberculous cystitis, almost invariably secondary to renal tuberculosis. They may be cases in which at the outset the diagnosis of unilateral surgical tuberculosis was satisfactorily made and nephrectomy done. Sometimes the tuberculous cystitis never subsides to an extent to allow of reasonable comfort. More commonly there is a period, sometimes for some years, of partial or extensive relief, to be followed by a recrudescence of the cystitis, perhaps associated with development of tuberculosis in the remaining kidney, but sometimes, at least, in the presence of a still uninfected kidney. In this group should also be included a small number of cases in which tuberculous urethritis with the development of multiple fistulae has rendered the patient's condition intolerable. The group of cases which may be considered suitable for diversion of the urinary stream are those in which the bladder condition is intolerable. Urinary frequency, and perhaps strangury, veto anything approaching comfortable existence, and the patient is condemned to torture during his remaining days. These patients may from the outset have a bilateral renal tuberculosis, but in any case many of them will live in torture for years, and are entitled to the relief which can be obtained by diversion of the urine. In this group of cases and in the preceding one, bladder drainage by suprapubic cystostomy fails to give satisfactory relief. It is further important to remember that the ureter of the remaining kidney when nephrectomy has been performed for tuberculosis is frequently abnormal, often showing considerable dilatation, apparently due to the increased thickness of the bladder wall through hypertrophy produced by frequency of urination. Obviously for this condition cystostomy will not be satisfactory.

5. *Cancer of the Bladder.*—Finally, one comes to the relatively large group of cases of cancer of the bladder in which the growth encroaches or certainly will encroach upon one or both ureters, and in which even the satisfactory removal or destruction of the tumor will still fail to relieve the patient. For some of these situations in which resection of the bladder wall is thought desirable, reimplantation of the ureter offers a satisfactory solution. In a not inconsiderable group, however, it is becoming increasingly apparent that nothing short of total cystectomy is at all likely to result in cure, and to the extent that we can with reasonable safety and reasonable comfort divert the urinary stream, to that extent the feasibility of total cystectomy will be increased. It is not intended here to discuss the very complicated problem of treatment of the more malignant bladder tumors. It is only suggested that there is wide agreement that for a considerable number, and perhaps for an increasing proportion, diversion of the urinary stream, with or without total cystectomy, is indicated.

METHODS OF DIVERTING THE URINE ABOVE THE LEVEL OF THE BLADDER

Having thus indicated the field for which diversion will be valuable, we must next turn to the methods at our disposal. At the present time they are three. We may divert the urine at the level of the kidney—nephrostomy. We may divert the urine by implantation of the ureter into the large intestine —uretero-enterostomy. We may bring the ureter out to the surface of the abdomen—cutaneous ureterostomy.

ADVANTAGES AND DISADVANTAGES OF THESE METHODS

1. *Nephrostomy.*—Since we believe that nephrostomy for anything but very temporary diversion is to be preferred to pyelostomy, this latter method is not here discussed. Nephrostomy diverts the urine at the level of the kidney. It has the advantage over all other methods in that it does not involve the division of the ureter, and does not, so to speak, burn one's bridges. It may therefore be employed as an intermediate stage, when, owing to the patient's condition, such as the recent proximity of a serious abdominal operation, no rearrangement of the ureter can properly be undertaken. It may be undertaken deliberately in the presence of damaged ureters in order to improve the condition of the kidneys, and perchance of the ureters, so as to make some further operation upon those structures reasonably safe. Properly done nephrostomy provides excellent drainage, though if the ureter be still patent, as will be the case as a rule, it does not entirely divert the urinary stream in most cases. It is an operation which can be relatively rapidly done, and with a relatively low mortality. If it is contemplated to make the diversion permanent, nephrostomy is a somewhat inconvenient arrangement for the patient, and, though he may learn to care for himself in a reasonably satisfactory manner, such is not always the case. Probably the greatest claim of nephrostomy is as a temporary measure, though if the measures contemplated for relief of the condition of the ureter should fail, it can always, so to speak, be made permanent. The mortality from the operation itself is difficult to state in precise terms, since it is intimately involved with the condition of the kidneys upon which the nephrostomy is undertaken. In and of itself it can be quickly and easily done, and should not involve a mortality of more than 5 per cent.

2. *Entero-Anastomosis.*—This is a method which has gained rapidly in favor since the technic suggested by Coffey,[6] of oblique introduction of the ureter into the bowel, has been generally used. The previous methods of which the Stiles[18] operation was perhaps the best example appear in the light of developments of the last ten years to involve a higher mortality, greater severity of renal infection, and a less permanently satisfactory condition of the patient.

In the following discussion we shall therefore assume that the principle of oblique implantation advocated by Coffey[3] is the method of election, though there are a variety of technics, some of which at least are too recent to warrant satisfactory appraisal. At the outset it should be recognized that entero-

anastomosis involves the division of the ureter, and its permanent disconnection from the bladder. To this extent it is more radical than nephrostomy. It is next important to appreciate that the operation is technically difficult and requires familiarity with the surgery of the urinary, as well as the intestinal, tract. The outstanding danger is that of infection, whether immediately, in connection with the operation (a risk which has been steadily diminishing with improved technic), or at various subsequent periods due to an ascending ureteritis and pyelonephritis which in the past has often been subject to periodic exacerbations.

It is perhaps proper here briefly to examine the claim put forward by Coffey[3] and others as to the method by which this oblique transplantation produced its results. It is not, we believe, anywhere suggested that there is

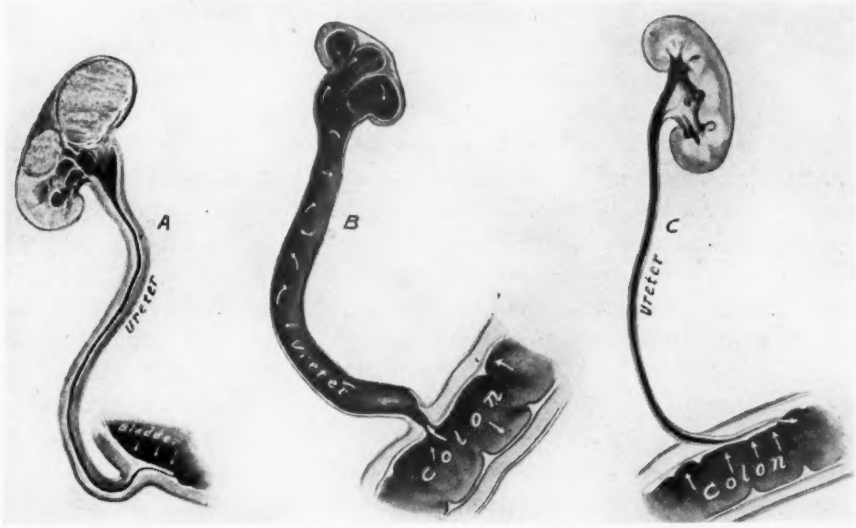

FIG. 1.—The *modus operandi* of so called "ascending infection." (*A*) What probably happens in experiments wherein infectious material is injected around the ureter near the bladder, true ascending infection following the lymphatic structures. (*B*) Dead kidney; dilated ureter following direct implantation of the ureter into the colon. This result usually has been referred to as "ascending infection." It is more probable that the kidney has been destroyed and the ureter dilated by static intra-intestinal pressure applied inside the ureter. (*C*) Normal kidney and undilated ureter which follow submucous or indirect implantation of the ureter into the colon (after Coffey).

created by this method anything which resembles the sphincteric mechanism of the ureterovesical orifice. Coffey[4] in his earlier papers described and illustrated his theory that the closure of the ureter in its oblique course through the bowel wall was effected by distention of the bowel, and that there was thus avoided the gaping orifice which had probably been associated with the direct methods of transplantation. He suggested that there was created here a valve which was closed by any condition tending to produce distention of that portion of the gut into which the ureter had been introduced (Fig. 1). It is difficult for us to appreciate how any such action can take place. A distention of the bowel sufficient to close the orifice would seem to us unlikely

to exist during most of the time. On the other hand, there is no force which tends to create back pressure upon the opening into the intestine, since it is unlikely that the accumulation of urine in the rectum will be sufficient to put the bowel wall on a stretch to any serious degree. Whatever may be the mechanism, it seems quite certain that our results as regards infection of the upper urinary tract to a serious or fatal degree have rapidly diminished since the introduction of this technic.

More recently a variety of methods have been suggested following the third type of operation suggested by Coffey[5] in which he did not produce immediate communication between the ureter and the intestine, but, by the introduction of a suture through the wall of the ureter and the mucous membrane of the intestine, allowed this to develop in the course of a few days as the suture cut through. At the time of his death, we believe, he advised the use of this technic for one ureter, leaving the other in open communication with the bowel by means of the catheter which he regularly employed. This suggestion of Coffey's[5] has been followed up by other writers, notably Higgins,[8] Zollinger,[20] and Poth.[15] The purpose of these alterations in technic is to avoid the infection which it is believed inevitably takes place from the exposure of the cut end of the ureter to the infected interior of the bowel. Most of the work, including that of Coffey, is either experimental or includes only a relatively small number of patients—too few to warrant safe conclusions. Clearly a considerable period of time should elapse before we can safely assume that these methods of what might be called the two stage anastomosis with the intestine do not involve the creation of an amount of scar tissue around the opening which at a subsequent period will contract and produce stricture. Such an eventuality is to be feared from what we know of the tendency of small openings in the side of the ureter to undergo some measure of closure. Only the lapse of some years can safely determine this point. Moreover, we are by no means clear that any of these methods do in fact insure to a high degree against ascending infection. We have progressively come to the view that ascending infection takes place by continuity along the ureter and does not take place along the periureteral lymphatic trunks which are segmental and not continuous. It is not clear to us that the slow cutting through of a ligature or similar method will in fact completely close the tissues of the ureter and insure against ascending infection. In fact this seems to us relatively unlikely, and we have seen no convincing evidence that implantation of the ureter into the large intestine by any method entirely and permanently avoids infection by the ascending route. That the infection is, by the use of modern methods, very much less than it used to be, that in a handsome proportion of cases it is trivial, and that adjustment to it takes place, seems to us quite clear. There are now at our disposal a considerable group of patients in whom the general principles of the Coffey technic have been used in which the operation was done more than 15 years ago. It is beyond question that the condition of these patients is enormously superior to that which we used to see following previous methods, but we do not think

we can safely assume that the kidneys of these patients are wholly free from infection and will remain so.

Another not inconsiderable objection, though one which in our judgment does not at all invalidate the usefulness of the procedure is the entire inaccessibility of the ureter once the implantation has been done and the catheters, if such have been used, have come away. Should serious infection supervene, or should obstruction slowly occur with the development of hydronephrosis, and its sequel pyonephrosis, our hands are tied as far as relieving the condition through the ureter is concerned. We may of course resort to nephrostomy if the situation warrants it, but at best we are in a weak position if these unfavorable developments occur.

Against these qualifications and difficulties must be placed the fact that satisfactory entero-anastomosis having been carried out, the patient is dry, clean, and comfortable. Furthermore, as already pointed out, there is accumulating evidence that these patients go on in comfort with kidneys, which if not sound, are at least sound enough for practical purposes for a period of many years. There can be no doubt that in properly selected cases, and in capable hands, uretero-enterostomy is an operation of first class importance.

We have postponed any discussion of the mortality because it is so difficult to give any clear and useful statement. Few very large series of comparable cases have been reported, and the conditions for which the operation was undertaken vary through a wide range. The selection of cases has been made very variously by different surgeons and in different countries, all of which makes any clear statement as to the risk verge on the impossible. It is curious, but apparently true, that of the cases reported in Europe the mortality in considerable groups is importantly higher than in the groups reported in this country. Thus Smitten[17] collected 316 cases of uretero-enterostomy in Europe with a mortality of 36.87 per cent. In the group of cases in which the transplantation was done for cancer, the mortality was 63.8 per cent. Papin[13] collected a series of 81 cases of uretero-enterostomy for cancer of the bladder with a mortality of 59.2 per cent. With this may be compared a group of 66 cases reported from The Mayo Clinic with a mortality of 16.6 per cent, and a subsequent report from the same clinic by Walters[19] of 76 cases with a mortality of 3.9 per cent. In these cases from The Mayo Clinic few if any cases of cancer of the bladder were treated by this method. Coffey[6] reported 18 cases of non-malignant conditions with a mortality of 11 per cent, and 17 cases of cancer with a mortality of 29.4 per cent. Nitch[12] reports six cases of non-malignant conditions with a mortality of 16.6 per cent and 14 cases of cancer with a mortality of 64.3 per cent. This perhaps gives as fair a picture as can be obtained in this complicated field. It at once appears that entero-anastomosis undertaken for cancer of the bladder has everywhere shown a mortality greatly in excess of that which follows its use in non-malignant conditions.

Cutaneous Ureterostomy.—This operation was first undertaken a good many years ago. It was apparently first proposed by Gigon[7] in 1856, and

first carried out shortly thereafter by LeDentu.[10] Like uretero-enterostomy it involves complete separation of the ureter from the bladder, and to this extent is permanent. It is technically an easy operation as compared with uretero-enterostomy, and the drainage is good if properly managed. The danger of infection is probably not greater than that involved in intestinal anastomosis, and should a severe infection occur, the ureter is accessible for irrigation and drainage. It is particularly applicable to the abnormal ureter. In fact, the grossly abnormal ureter is more easily managed by this technic than the normal one. Opposed to these desirable characteristics is the fact that the patient is required to wear an apparatus for reception of the urine, and has to take care of a small, though always present, dressing. It is not true, as has been commonly supposed, that these patients cannot be kept dry, and are consequently more or less malodorous. With good technic and proper management, an entirely dry, clean diversion can be had, and the patients may lead normal lives without social embarrassment.

In 1913, Schichkoff[16] was able to collect 43 cases of cutaneous ureterostomy. Twenty unilateral cases showed a mortality of 10 per cent. Twenty-three bilateral cases showed a mortality of 26 per cent. The bilateral cases were all cases of cancer which perhaps explains the mortality. Papin[14] reported a series of 96 cases of his own and other surgeons in which operation was done for malignant tumors, tuberculosis, and malformations of the bladder with a mortality of 24.9 per cent.

The operation seems to have been done more commonly in Europe than in this country, perhaps because of the above suggested high mortality of uretero-enterostomy. The question of the duration of life after cutaneous ureterostomy is difficult to state. The majority of patients for whom it has been done have been subjects either of cancer or tuberculosis. Now obviously either of these diseases is likely to kill the patient within the next ten years, although in the case of the patient with a non-tuberculous remaining kidney and an intolerable tuberculous cystitis, survival may take place for many years. Keyes[9] recently reports one of more than ten years. The cases thought suitable for cutaneous ureterostomy will as a rule have damaged ureters and more or less damaged kidneys. This situation cannot be compared satisfactorily with the patients for whom uretero-intestinal anastomosis is undertaken, since they should in the majority of cases have normal ureters and normal kidneys. One group starts from scratch with a normal urinary apparatus above the bladder, the other starts with a tremendous handicap of disease which in the case of cancer and tuberculosis will in the normal course of events be fatal in any case. To this extent the expectancy of life as concerns the two operations is difficult to compare.

CHOICE OF OPERATIONS AND TECHNIC

Nephrostomy.—To summarize what has above been said—nephrostomy is perhaps at its best as a temporary expedient to bridge the gap so that a more permanent arrangement such as reimplantation of the ureter into the

bladder, possibly uretero-ureteral anastomosis or uretero-intestinal anastomosis may be carried out. It will thus be useful in the case of ureters injured at an operation in which the condition of the patient does not justify further prolonging it or in which the injury to the ureter is not discovered until subsequent days. It will be useful in ureterovaginal fistulae developing at some distance following a pelvic operation, as for instance, hysterectomy, either for malignant or benign tumor. The same applies to various other operations in the pelvis in which injury to the ureter occasionally takes place. Its chief function is in making postponement of the final adjustment of the urinary tract possible. In regard to technic, the method suggested by us in conjunction with our colleague, W. W. Holland,[2] in 1932, has stood us in good stead. It can be carried out without extensive mobilization of the kidney, it avoids unnecessary damage to the kidney, and prevents the traumatic bleeding which has in the past blocked tubes and caused annoyance.

Uretero-Enterostomy.—The most favorable group of cases are those in children with exstrophy or epispadias in which the ureters are normal. For these patients with the appropriate technic, I believe that the operative mortality should be well below 5 per cent. The next most favorable group will be in those patients in whom the bladder is seriously involved, but in which the ureters have remained normal. This will include chiefly the patients in Group 2 above referred to—that is to say those with vesicovaginal fistulae, and in Group 3, those with non-tuberculous chronic interstitial cystitis. Here if the ureters are normal and the operation well executed, a low mortality can be expected. Patients with cancer present a difficult problem. In the earlier stages, even with growths situated, as they most commonly are, in the base of the bladder, there may be no involvement of either ureter. To this extent the conditions for uretero-enterostomy are favorable. On the other hand, it is at least desirable to subject these patients to as few operative procedures as possible. For this reason both ureters must be moved at the same sitting, and it is eminently desirable that the bladder should be removed at the same time. This is a formidable procedure and will test the skill and dexterity of the surgeon as well as the resisting powers of the patient. Most of them are old. The presence of cancer seems in some mysterious way to lower their vitality, and we fear that the mortality will long remain higher than among those patients with normal ureters but without cancer. The first principle exemplified by the low mortality in children and in adults with non-malignant bladder lesions is that the implantation of a normal ureter is not a severe proceeding. The next principle is that simultaneous bilateral transplantation is importantly more risky than if one ureter is moved at a time. The lowest mortality can be obtained by doing the operation in two stages and making the operation substantially extraperitoneal, as in the operation first described by C. H. Mayo, which one of us (Cabot[1]) has consistently employed for such cases for 15 years and in which the mortality should not exceed 3 per cent. This method is feasible and desirable in most of the patients without cancer,

but in the presence of cancer subjects the patient to a multiplicity of operations which may well turn the scale against him.

When one comes to consider the implantation of abnormal ureters, the case is very different. Given gross abnormality with dilatation and hypertrophy of the ureter, entero-anastomosis takes on a risk which in our experience has rarely been justified. Now it is occasionally possible to minimize this risk by combining nephrostomy for kidney drainage with a subsequent uretero-enterostomy carried out during diversion of the urinary stream at the kidney level. Done in this way we have been able successfully to transplant five ureters in three patients without mortality. It is probably applicable chiefly to those patients in whom there has been accidental injury to the ureter and for whom uretero-ureterostomy or ureterovesical implantation are unsuitable. For them nephrostomy and subsequent uretero-enterostomy may be the method of choice. With this exception it seems that experience at least suggests that the grossly abnormal ureter is rarely suitable to this method of management.

Summarized, the transplantation of the normal ureter carries a relatively low mortality. If the operation can be done in two sittings, as is suitable for exstrophy, epispadias, vesicovaginal fistula, chronic interstitial cystitis with normal ureters, a very low mortality can be expected. Bilateral simultaneous transplantation will always give a somewhat greater risk, but in good hands and with normal ureters, is a satisfactory procedure.

Cutaneous Ureterostomy.—This appears the method of election for the great majority of cases with grossly abnormal ureters. It is quite certainly the method of election for patients with vesical tuberculosis of an intolerable and intractable type, whether the kidney lesion be a bilateral, inoperable tuberculosis, tuberculosis of a remaining kidney after nephrectomy, or as not rarely occurs, in the presence of an intractable bladder lesion but with a remaining kidney normal except for some dilatation and atony of the ureter. For these patients immense relief may be expected. The duration of life will of course depend upon the condition of the kidneys as concerns infection with tuberculosis.

For patients with cancer in whom total cystectomy is considered or in whom the bladder lesion has involved one or both ureter orifices and is endangering kidney function, cutaneous ureterostomy seems the method of choice. It is a relatively easy operation with low mortality. It can safely be combined with total cystectomy if the situation is favorable. It can be done as a preliminary to total cystectomy without complicating the approach to the bladder, and the cystectomy can be undertaken relatively shortly after the diversion of the urinary stream.

In regard to the technic, we think it important that the ureter should be made to lead straight from kidney pelvis to point of exit in the skin (Fig. 2). We believe it desirable to bring the ureter out at a point considerably higher than is commonly employed, namely at about the level of the anterior iliac spine. Done in this way the blood supply of the ureter is better and there is less ureter involved. We think it important to free the ureter in such a

way that it will project for some distance beyond the skin after the wound is closed, and that the ureter should not be attached to any of the underlying tissues for fear of injury to the ureter with the development of scar and fistula (Fig. 3). Dry, comfortable diversion can be best obtained by keeping a catheter of appropriate size permanently in the ureter, its point lying com-

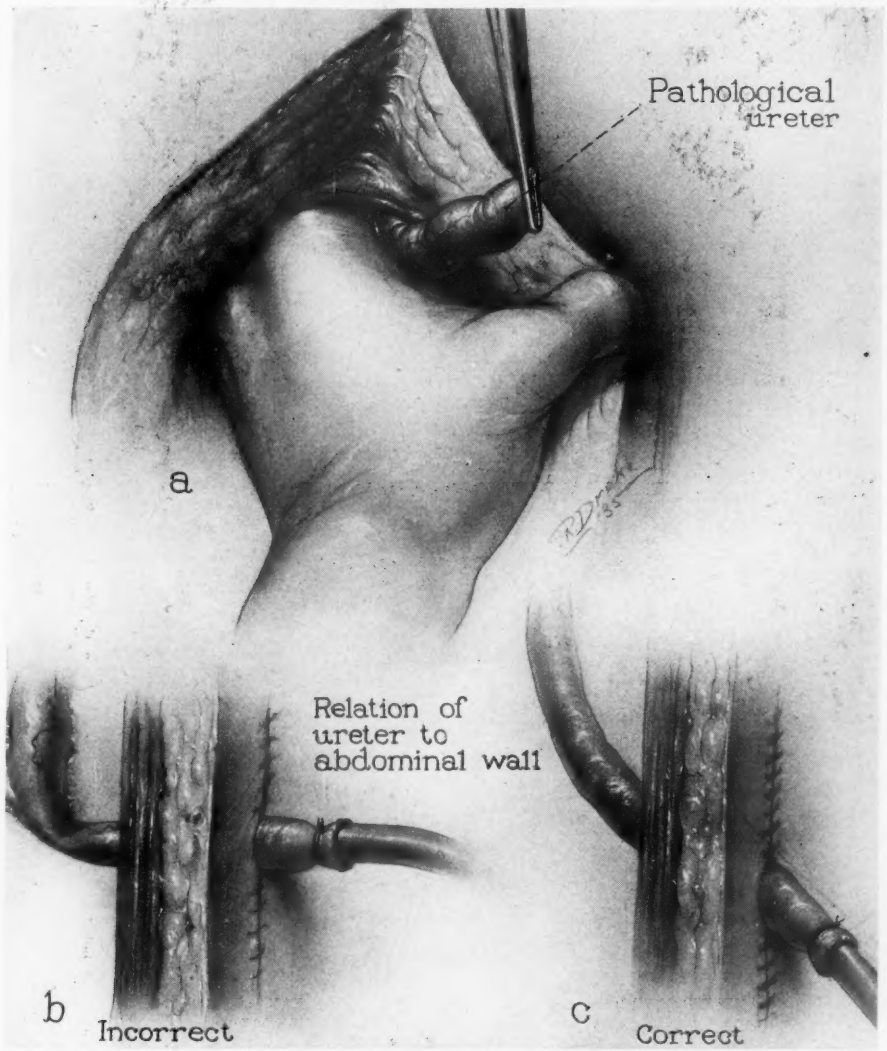

FIG. 2.—These drawings illustrate two important points: (1) (*a*) shows the freeing of the ureter upward toward the kidney in order to eliminate kinks and twists which are so commonly present; (2) (*b*) and (*c*) illustrate the incorrect and correct methods of bringing the ureter through the tissues of the abdominal wall.

fortably within the renal pelvis. In this way dryness can be achieved, which is very difficult by the employment of any form of apparatus or cup designed to fit snugly over the orifice. Moreover, the constant presence of a catheter in the ureter will avoid the development of stricture, which is liable to occur at the point of exit from the skin (Fig. 4). This complication can, we think,

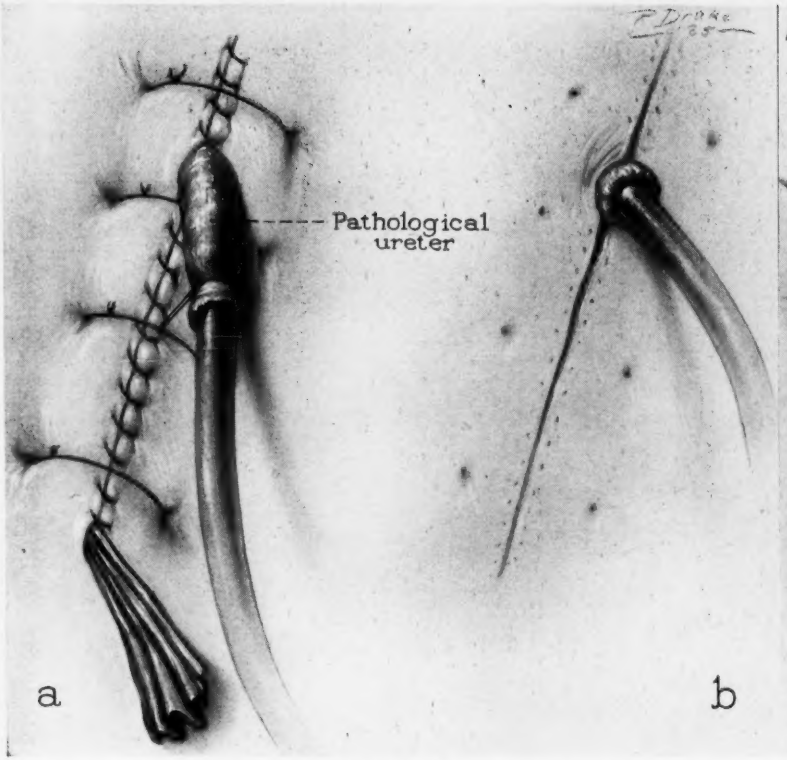

FIG. 3.—(*a*) Shows the method of holding the tube in the ureter by a tie placed about it, and the avoidance of attachment of the ureter to the skin. If there is danger of tension, the ureter may be attached indirectly to one of the sutures, closing the abdominal wound. (*b*) Shows the condition of the stump of the ureter ten days after ureterostomy. It illustrates the level at which sloughing takes place and the way in which the mucous membrane of the ureter everts so as to prevent stricture.

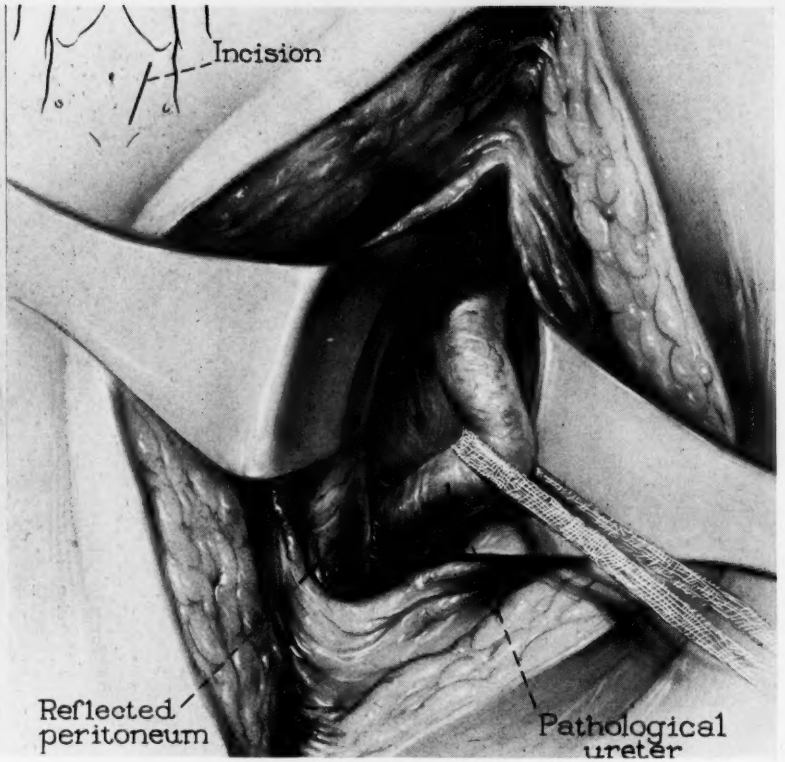

FIG. 4.—Shows the appearance of the grossly abnormal ureter which is commonly to be dealt with in this operation. The insert, upper left, shows the position of the incision.

often be avoided by the method of leaving the ureter projecting beyond the skin at the time of operation, and allowing it to slough off, which it will ordinarily do, leaving a pouting rosette of mucous membrane which guards

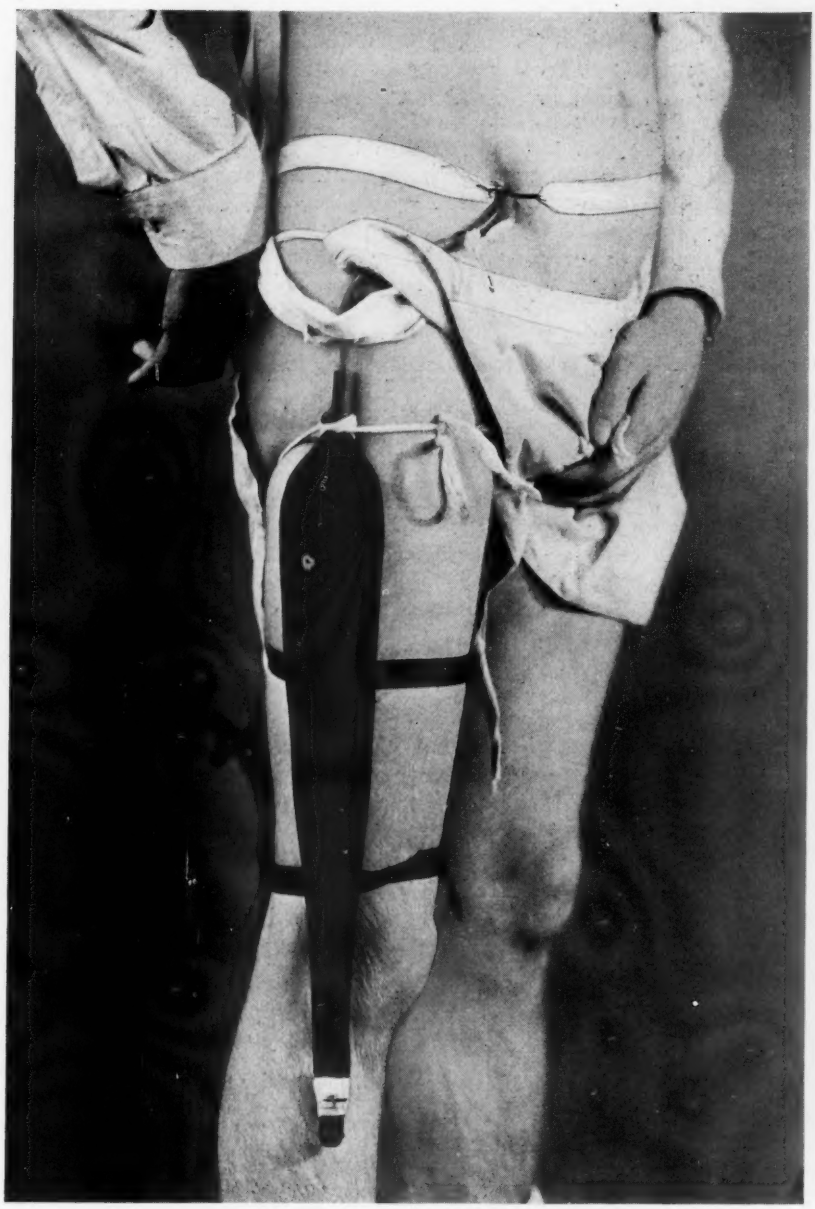

FIG. 5.—Illustrates the type of apparatus actually used by a patient with a single remaining kidney 18 months after ureterostomy for intractable vesical tuberculosis.

the orifice. The catheters thus employed may be led either into small hot water bottles suspended from a belt or to the long narrow rubber urinals which have been employed in the past for patients with incontinence (Fig. 5).

If reasonable care is taken in regard to cleanliness of the rubber receptacles, complete absence of disagreeable odor can be assured.

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DIVISION OF THE SPERMATIC CORD AS AN AID IN OPERATING ON SELECTED TYPES OF INGUINAL HERNIA

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COMPLETE division of all the structures comprising the spermatic cord, as an aid in the cure of certain types of inguinal hernia, appears to be a most radical procedure. Orchidectomy has been resorted to occasionally to eliminate the weak spot caused by the emergence of the cord in multiple recurrences; and it occurred to us that if we could divide the cord without causing subsequent sloughing of the testicle, the operation would be expedited and a more perfect repair obtained. We had observed patients in whom, at operation, the vessels had been practically destroyed without necrosis of the gland; and we finally decided to divide the cord deliberately, and were gratified to find that the testicle did not slough.

The following indications, in our opinion, justify this radical procedure:

(1) Recurrent herniae which have had one or more unsuccessful attempts at a radical cure in individuals past 50 in whom the opposite testicle is apparently normal.

(2) Recurrent herniae in younger subjects who are incapacitated from their usual occupation, and who have an apparently normal testicle on the opposite side. These patients have usually had more than one attempt made at a repair; and if, at operation, division of the cord offers a more favorable prognosis, we do not hesitate to divide it.

(3) Large scrotal herniae in the aged, which are either irreducible or cannot be satisfactorily retained by a truss.

(4) Large sliding herniae.

Division and resection of a part of the cord reduce the operating time at least a third. Furthermore, it permits two layers of muscle or fascia to be sutured to Poupart's ligament without any intervening tissue, and without leaving a weak spot in either layer which of necessity exists if the cord is present.

In order to obtain the maximum benefit in time-saving, the cord must be divided early in the operation. We make our decision as soon as the sac has been isolated. A ligature is placed about the cord at its emergence through the internal ring, and a second one as it enters the scrotum, the intervening tissue being excised. The collateral circulation is limited and we believe that the lymphatic supply must aid in nourishing the gland until the arterial supply is sufficiently reestablished. In scrotal herniae it is unwise to disturb the lower end of the sac for fear of damaging the future collateral circulation; and we make it a practice never to deliver the testicle into the wound or to remove the scrotal portion of the sac.

ANALYSIS OF CASES OF DIVISION OF THE CORD IN THE REPAIR OF INGUINAL HERNIA

No.		Age	Diagnosis	Operation	Date	Wound Healing	Followed	Hernia Wound	Testicle	Remarks
1	FK	62	ROIH scrotal	Gallie	1/17/28	P.U.	12/11/29	O.K.		Induration of scrotum for five months
2	AG	67	ROIH scrotal	Gallie	11/ 2/28	P.U.	12/ 3/28	O.K.		
3	JW	65	RDIH recurrent	Gallie	11/22/28		11/25/28			Died third day, pneumonia
4	MM	43	RDIH recurrent	Gallie	1/15/29	P.U.	10/21/29	O.K.		
5	AM	59	LOIH sliding	Ox fascia	3/ 5/29	Slight serous drainage	4/12/29	O.K.		
6	GS	79	ROIH	Ox fascia	3/ 7/29	P.U.	7/ 8/34	O.K.	Slight atrophy	
	GS		LOIH	Ox fascia	3/ 7/29	P.U.	7/ 8/34	O.K.	Slight atrophy	
7	HJ	45	LOIH sliding	Ox fascia	3/14/29	P.U.	4/ 5/29	O.K.		
8	AR	58	ROIH recurrent	Ox fascia	3/19/29	P.U.	10/ 3/30	O.K.	Normal	
9	WV	30	ROIH recurrent	Gallie	4/23/29	P.U.	9/12/32	O.K.		
10	SS	55	ROIH incarcerated	Ox fascia	5/ 9/29	P.U.	5/27/29	O.K.		Slight swelling of scrotum
11	WD	64	RDIH recurrent	Ox fascia	6/26/29	Drained at operation. Healed in one month	9/23/29	O.K.		
12	JK	60	LOIH scrotal	Ox fascia	9/ 3/29	P.U.	11/17/31	O.K.	Atrophied	
13	JP	65	ROIH	Ox fascia	9/10/29	P.U.	11/16/31	O.K.		Induration of scrotum for two months
14	ES	49	ROIH scrotal irreducible	Gallie	9/30/29	P.U.	12/ 2/31	O.K.		
15	RG	41	LDIH recurrent	Ox fascia	10/ 8/29	P.U.				
16	FA	65	ROIH scrotal	Gallie	10/22/29	P.U.	2/26/30	O.K.		
17	HG	39	ROIH scrotal irreducible	Gallie	12/ 3/29	P.U.	1/ 3/30	O.K.		
18	JR	67	RDIH recurrent	Ox fascia	12/10/29	Mild infection	2/26/32	Recurrence	One-half normal	
19	PH	52	LOIH sliding	Gallie	12/10/29	P.U.	12/12/34	O.K.	Normal	
	PH		ROIH sliding	Gallie	12/10/29	P.U.	12/12/34	O.K.	Normal	
20	JC	58	LOIH recurrent	Gallie	12/17/29	P.U.	1/15/30	O.K.		
21	UA	55	RDIH recurrent	Gallie	12/27/29	P.U.	2/24/30	O.K.		
22	PL	44	RDIH	Gallie	1/ 7/30	P.U.	6/26/30	O.K.		
23	MF	57	LDIH	Ox fascia	2/11/30	Mild infection	3/ 1/35	O.K.		
24	AL	56	LOIH recurrent	Ox fascia	2/18/30	Infected 18 days	9/11/31	Recurrence	Normal	3/10/35 same
25	MH	45	RDIH recurrent	Gallie	2/18/30	P.U.	3/25/30	Recurrence		8/11/34 same
26	EW	73	RDIH recurrent	Gallie	3/18/30		3/21/30			Died third day, pneumonia
27	GB	59	LOIH sliding	B	6/ 3/30	P.U.	12/10/34	O.K.	Normal	Small hydrocele
28	RW	55	ROIH sliding	Gallie	6/17/30	P.U.	7/ 9/30	O.K.		Marked swelling of scrotum
29	JC	68	ROIH scrotal	B	7/15/30	P.U.	9/26/30	O.K.		
30	PF	52	RDIH recurrent	Gallie	7/15/30	P.U.				
	PF		LDIH recurrent	Gallie	7/15/30	P.U.				
31	EP	50	ROIH	Gallie	7/29/30	P.U.	12/ 9/31	O.K.		
32	FC	50	LOIH scrotal irreducible	Gallie	7/29/30	Infected three weeks	2/ 1/34			Died of pneumonia, three and one-half years
33	PS	65	ROIH scrotal	B	8/12/30	Late infection. Healed after suture sloughed	11/24/30	O.K.		

34	JH	59	LOIH scrotal recurrent	Ox fascia	8/19/30	P.U.	5/13/31	O.K.	Normal	
35	CR	55	RDIH strangulated	Ox fascia	9/15/30	Mild infection	11/17/31	O.K.	Normal	
	CR		LDIH scrotal	Ox fascia	9/30/30	Slight infection	11/17/31	O.K.	Normal	
36	JC	54	LOIH	Ox fascia	9/16/30	Hematoma of scrotum, drained seventh day	2/25/31	Recurrence		Reoperated 10/13/31
37	JD	76	RDIH scrotal	Ox fascia	9/23/30	Hematoma of wound, drained seventh day	10/14/34	O.K.	Normal	
38	MP	40	ROIH	Gallie	9/23/30	P.U.	12/ 4/31	O.K.		
39	CQ	63	ROIH scrotal	Ox fascia	9/25/30	Slight infection	10/14/34	O.K.		
40	PV	45	RDIH recurrent	Gallie	10/14/30	P.U.	2/ 8/31	Recurrence		10/14/34 same
41	LT	66	ROIH	Gallie	11/11/30	P.U.	2/20/33	O.K.		
42	JS	34	RDIH recurrent	Gallie	11/23/30	Postoperative hemorrhage, packed	2/ 9/34	O.K.		
43	FP	58	RDIH recurrent sliding	Gallie	12/ 2/30	P.U.	12/26/30	O.K.		
44	HS	80	ROIH scrotal	B	12/18/30	Deep abscess	12/29/30			Died 11th day, peritonitis
45	MS	39	LOIH incarcerated	Ox fascia	1/27/31	P.U.				
46	JH	58	ROIH	Ox fascia	2/17/31	P.U.	11/14/34	O.K.		
47	FE	70	LOIH	B	3/10/31	P.U.	9/ 4/31	O.K.	Olive size	
48	ML	44	ROIH recurrent	Gallie	4/ 7/31	Drained at operation. Healed in one month	4/ 1/32	O.K.	Normal	
49	LC	59	ROIH	Ox fascia	4/14/31	P.U.	7/10/31	O.K.		
50	WS	67	ROIH	B	4/21/31	P.U.	5/11/31	O.K.		
51	JD	54	ROIH	Gallie	5/12/31	P.U.	5/21/33	O.K.		Died—heart disease two years
52	AF	63	RDIH	Ox fascia	5/12/31	P.U.	11/30/31	Recurrence	Large and hard	
53	CD	49	ROIH scrotal	B	5/26/31	P.U.	12/ 4/31	O.K.	Normal	Testicle swollen three months
54	LS	45	LOIH sliding	Hotchkiss	6/26/31	P.U.	10/23/31	Recurrence		10/19/34 same
55	TR	48	LDIH recurrent	Gallie	7/24/31	P.U.	10/31/34	Recurrence		
56	AD	63	LDIH	Gallie	8/ 4/31	Infected, drained 16th day	10/ 2/31			Still draining
57	AG	52	ROIH	B	8/15/31	P.U.	9/ 2/31	O.K.		
58	MR	74	LOIH scrotal irreducible	B	9/ 2/31	P.U.	1/21/33	O.K.	Normal	Died fractured skull 16 months later
	MR		ROIH scrotal irreducible	B	9/ 2/31	P.U.	1/21/33	O.K.	Normal	
59	JS	68	ROIH strangulated	B	9/ 2/31	Mild infection	1/12/35	O.K.	Atrophied	
60	CG	62	ROIH scrotal irreducible	Ox fascia	9/ 8/31	Suppuration—three weeks	12/ 8/31	Recurrence		
61	EC	70	LOIH scrotal	B	9/ 8/31	P.U.	2/24/32	O.K.	Normal	
62	AS	65	ROIH scrotal	B	10/29/31	P.U.	12/ 2/31	O.K.		
63	MN	55	ROIH scrotal	B	11/16/31	Suppuration—three weeks	2/ 2/35	O.K.	Normal	
64	AF	61	LOIH	Gallie	1/ 5/32	P.U.	10/20/34	O.K.		
65	TS	62	RDIH	B	2/16/32	P.U.	2/17/35	O.K.	Normal	
66	KK	31	ROIH recurrent	Gallie	3/ 7/32	P.U.	5/27/32	O.K.		
67	MN	28	RDIH recurrent	Gallie	3/22/32	P.U.				

ANALYSIS OF CASES OF DIVISION OF THE CORD IN THE REPAIR OF INGUINAL HERNIA—*Continued*

No.		Age	Diagnosis	Operation	Date	Wound Healing	Followed	Hernia Wound	Testicle	Remarks
68	BS	43	RDIH	Gallie	4/ 8/32	P.U.	10/14/34	O.K.		
	BS		LDIH	Gallie	4/ 8/32	P.U.	10/14/34	O.K.		
69	JM	54	ROIH	B	4/12/32	P.U.	5/15/32	O.K.	Swollen	
70	MO	57	LDIH	Gallie	5/ 3/32	P.U.	7/ 1/32	O.K.	Slight atrophy	
	MO		RDIH	Gallie	5/ 3/32	P.U.	7/ 1/32	O.K.	Slight atrophy	
71	AU	58	LOIH	B	5/24/32	P.U.	6/15/32	O.K.		
72	IZ	65	RDIH	B	7/12/32	P.U.	2/17/35	O.K.	Three-fourths normal	
	IZ		LOIH	B	7/12/32	P.U.	2/17/35	Recurrence	Normal	
73	WL	64	ROIH scrotal	B	7/25/32	P.U.	8/15/32	O.K.	Normal	
74	AC	64	RDIH	B	7/29/32	P.U.				
75	HN	59	ROIH	B	7/29/32	P.U.	2/23/35	O.K.	Normal	
76	GF	57	LOIH sliding	Hotchkiss	8/ 8/32	P.U.				
77	DG	63	ROIH irreducible	B	9/20/32	P.U.	3/19/35	O.K.	Normal	
78	HL	73	ROIH recurrent	B	9/20/32	P.U.	10/11/32	O.K.		
	HL		LOIH	B	9/20/32	P.U.	10/11/32	O.K.		Cord swollen
79	JM	55	ROIH scrotal	B	9/27/32	Drained at operation				
80	HD	34	LOIH irreducible	Gallie	11/15/32	P.U.	2/13/35	O.K.	One-half normal	Testicle swollen six weeks
81	HS	39	LOIH recurrent	Gallie	11/22/32	P.U.	11/ 4/34	O.K.	Atrophied	
82	MS	57	LDIH	Gallie	1/10/33	P.U.	1/30/33	O.K.		
83	HM	45	ROIH	B	1/26/33	P.U.	2/17/33	O.K.	Normal	
84	WB	33	LOIH recurrent	Gallie	2/23/33	P.U.	11/ 4/34	O.K.		
85	SM	46	LOIH recurrent	Gallie	3/ 7/33	Infected hematoma, drained eighth day				
86	ER	45	LOIH	B	3/22/33	P.U.				
87	MF	57	ROIH sliding	Gallie	4/ 4/33	P.U.	11/ 4/34	O.K.	Normal	
88	GS	57	ROIH	B	4/ 4/33	P.U.	5/ 8/33	O.K.		
89	HA	60	ROIH	B	4/11/33	P.U.	1/10/34	O.K.	Normal	
90	WW	48	LOIH scrotal	B	4/18/33	Deep infection	4/22/33			Died fifth day, peritonitis
91	IK	56	LOIH scrotal	B	4/18/33	P.U.	5/29/33			Late scrotal abscess drained
92	EB	55	ROIH scrotal	B	4/18/33	P.U.	10/30/33	O.K.	Normal	
93	WW	47	LDIH recurrent	Gallie	5/ 2/33	P.U.	5/24/33	O.K.		
94	WW	58	ROIH	B	5/ 5/33	P.U.				
95	LN	60	LOIH	B	5/16/33	P.U.	7/14/33	O.K.		
96	JW	57	RDIH recurrent	Gallie	6/ 6/33	P.U.				
97	LC	49	LOIH recurrent	Gallie	6/ 6/33	P.U.	8/11/33	Recurrence	Normal	
98	JS	47	LOIH recurrent	Gallie	6/ 6/33	P.U.	6/28/33	O.K.		
99	LR	43	RDIH recurrent	Gallie	6/13/33	P.U.	8/16/33	Recurrence		

100	FS	56	RDIH recurrent	Gallie	7/11/33	P.U.	9/12/34	Recurrence	Normal	
	FS		LDIH recurrent	Gallie	7/11/33	P.U.	9/12/34	Recurrence	Normal	
101	SG	46	LDIH	Gallie	7/18/33	P.U.	8/ 9/33	O.K.		
102	SG	50	ROIH recurrent	Gallie	7/25/33	Extensive suppuration	11/ 4/34	O.K.	Removed	8/7/33 orchidectomy
103	DH	52	RDIH	Gallie	8/15/33	P.U.	11/ 7/34	O.K.	One-fourth normal	
104	MR	64	ROIH	B	8/22/33	P.U.	3/11/35	O.K.	Normal	
105	WB	73	RDIH	B	9/12/33	P.U.	10/20/33	O.K.	Swollen	
	WB		LDIH	B	9/12/33	P.U.	10/20/33	O.K.	Swollen	
106	JR	66	ROIH recurrent	B	10/24/33	P.U.	11/14/34	O.K.		
107	AS	62	LDIH	B	10/25/33	P.U.	12/12/33	O.K.	Normal	Testicle swollen one month
108	EK	64	ROIH scrotal	B	11/14/33	P.U.	1/31/34	O.K.	Enlarged	
109	GS	53	RDIH recurrent	Gallie	12/ 5/33	P.U.	11/ 4/34	O.K.		
110	AR	70	ROIH irreducible sliding	Hotchkiss	12/ 5/33	P.U.				
111	BS	52	LDIH	Ox fascia	2/ 7/34	P.U.				
112	WQ	58	LOIH sliding	Hotchkiss	2/17/34	P.U.	8/ 6/34	O.K.	Normal	
113	LC	62	ROIH	B	2/27/34	P.U.	12/26/34	O.K.	Normal	
114	PM	42	RDIH	Gallie	3/12/34	P.U.				
115	KH	49	RDIH recurrent	Gallie	3/13/34	P.U.	8/28/34	O.K.	Normal	
116	LC	60	LOIH	B	4/ 5/34	P.U.	2/18/35	O.K.	Removed	Hydrocele—9/19/34 orchidectomy
117	FP	48	LOIH	B	4/10/34	P.U.	5/ 2/34	O.K.	Swollen	
118	WW	55	RDIH recurrent	Gallie	4/10/34	P.U.	6/15/34	O.K.		
119	JL	57	ROIH	Gallie	4/17/34	P.U.	6/27/34	O.K.		
120	FP	77	LDIH	B	4/26/34	P.U.				
121	AD	51	ROIH scrotal	Gallie	5/22/34	P.U.	6/29/34	O.K.		Scrotum swollen for one month
122	RM	59	ROIH	B	6/12/34	P.U.	3/ 4/35	O.K.	One-half normal	Testicle swollen one month
123	EM	48	ROIH recurrent	Gallie	6/12/34	P.U.	8/10/34	O.K.		
124	TG	59	ROIH	B	6/20/34	P.U.	8/15/34	O.K.	Normal	
	TG		LOIH	B	6/20/34	P.U.	8/15/34	O.K.	Normal	
125	FW	67	LOIH	B	6/19/34	Infection 13th day	8/ 6/34			Draining, two sutures sloughed
126	WT	52	RD and OIH	Gallie	7/10/34	P.U.	9/14/34	O.K.		
127	HS	70	LDIH scrotal	B	7/31/34	P.U.	11/ 1/34	O.K.		Testicle swollen two months
	HS		RDIH	B	7/31/34	P.U.	11/ 1/34	O.K.		Testicle swollen two months
128	CM	55	LOIH	Gallie	8/28/34	P.U.	11/ 2/34	O.K.		
	CM		ROIH	Gallie	8/28/34	P.U.	11/ 2/34	O.K.		
129	VC	48	LDIH	Gallie	9/18/34	P.U.	11/ 2/34	O.K.		
130	HM	58	RD and OIH	Gallie	10/ 2/34	P.U.	12/ 7/34	O.K.	Swollen	
131	WS	65	ROIH	B	10/ 2/34	P.U.	11/12/34	O.K.		Testicle swollen one month
132	RG	33	ROIH recurrent strangulated	B	9/12/29	P.U.				
133	MR	38	LOIH recurrent	B	9/18/29	P.U.	3/23/33	O.K.		
134	PJ	29	LOIH recurrent	Gallie	3/27/30	P.U.	12/ 9/31	Recurrence		
135	JP	53	ROIH recurrent	Gallie	5/27/31	P.U.	12/16/31	Recurrence	Atrophied	Testicle swollen two months

ANALYSIS OF CASES OF DIVISION OF THE CORD IN THE REPAIR OF INGUINAL HERNIA—*Concluded*

No.		Age	Diagnosis	Operation	Date	Wound Healing	Followed	Hernia Wound	Testicle	Remarks
136	GH	47	LOIH recurrent × 3	Gallie	6/24/31	P.U.	11/27/34	O.K.		
137	LB	53	LOIH	W. Andrews	8/12/31	P.U.	9/ 8/31	O.K.		
138	MS	56	ROIH	B	8/12/31	P.U.	12/22/31	O.K.		
139	OK	53	RDIH	B	12/23/31	P.U.	1/12/32	O.K.		
140	PS	54	RD and OIH	W. Andrews	1/30/32	P.U.	2/18/35	O.K.	Two-thirds normal	Testicle swollen one month
141	TP	46	RDIH recurrent	B	5/18/32	P.U.	5/ 6/34	O.K.	Atrophied	
142	JM	61	LOIH scrotal irreducible	Gallie	4/12/33	Infection 17th day	12/18/34	O.K.	Removed	5/3/33 orchidectomy
143	WW	60	LDIH recurrent incarcerated	B	6/15/33	P.U.	6/ 3/34	Recurrence		11/10/34 same
144	WT	59	ROIH irreducible	B	3/ 9/34	P.U.	6/ 3/34	O.K.	Atrophied	
145	DS	69	LOIH sliding	Hotchkiss	3/16/34	P.U.	1/31/35	O.K.	Normal	
146	FR	47	RDIH recurrent	B	10/25/34	P.U.	3/ 5/35	O.K.		
147	FH	56	LDIH recurrent	Gallie	10/18/28	Mild infection, tenth day	1/ 6/29	O.K.		
148	FS	56	LOIH recurrent	Gallie	12/ 3/30	P.U.	10/26/33	O.K.	Normal	
149	FL	57	LDIH recurrent	Gallie	11/ 7/31	Infected third day	6/24/32	O.K.		Drained eight weeks
150	PS	66	RDIH	Gallie	5/ 9/31	Infected sixth day	8/28/31	O.K.		
	PS		LDIH	Gallie	5/ 9/31	Infected sixth day	8/28/31	O.K.		Drained four weeks
151	JD	55	LOIH recurrent	Gallie	5/16/31	Infected third day	12/27/34	O.K.	Normal	Drained five weeks
152	AK	51	RDIH recurrent	B	8/ 4/31	P.U.				
153	SS	44	ROIH scrotal	Gallie	9/19/31	P.U.	11/27/31	O.K.	Swollen	
154	JH	74	ROIH strangulated	B	9/30/31	P.U.	10/20/31	O.K.		Died 20th day, pneumonia
155	WF	54	LOIH scrotal	Gallie	8/ 5/32	P.U.				
156	JM	53	LOIH scrotal	B	7/29/32	P.U.	12/27/34	O.K.	One-half normal	
157	JM	69	ROIH sliding incarcerated	B	9/25/32	Drained at operation. Healed in 15 days				
158	SD	61	RDIH	Gallie	12/ 8/32	Drained at operation. Healed in 15 days	5/25/33	O.K.	Normal	

159	MP	56	RDIH recurrent	Gallie	12/ 2/32		12/ 6/32			Died fourth day, pneumonia
160	AS	42	LDIH sliding	Gallie	1/31/33	P.U.	3/29/34	O.K.	Atrophied	
161	JL	59	RDIH recurrent	Gallie	3/11/33	Drained at operation. Healed in ten days	12/27/34	O.K.	One-fourth normal	
162	JR	50	RDIH recurrent	Gallie	3/10/33	P.U.	12/27/34	O.K.	Normal	
	JR		LOIH	B	3/10/33	P.U.	12/27/34	O.K.	Normal	
163	TT	47	RDIH recurrent	Gallie	4/21/33	Infected tenth day				
164	AW	53	ROIH scrotal	B	5/12/33	P.U.				
165	HH	69	LOIH	B	6/13/33	P.U.	8/31/33	Recurrence		
	HH		ROIH	B	6/13/33	P.U.	8/31/33	O.K.		
166	HH	35	ROIH	B	7/ 5/33	Mild infection	6/28/34	O.K.	Normal	
167	AB	42	ROIH scrotal	B	7/ 7/33	P.U.				
168	JP	72	RDIH	B	9/26/33	P.U.	12/27/34	O.K.	One-half normal	
169	CE	70	ROIH scrotal incarcerated	B	7/ 8/33	Infected 35th day	12/27/34	O.K.	Removed	8/12/33 orchidectomy. Healed 12th week
170	PS	51	RDIH recurrent × 2	B	3/31/34	Hematoma third day. Healed 28th day	12/27/34	Recurrence	One-half normal	3/19/35 same
171	CF	63	LDIH	Gallie	6/15/34	P.U.				
172	AP	66	RD and OIH	B	7/ 3/34	P.U.	9/27/34	O.K.		
173	JB	41	ROIH	B	6/29/34	Infected seventh day	12/27/34	O.K.	Removed	7/17/34 orchidectomy. Healed seven days
174	WM	38	ROIH sliding	B	7/27/34	P.U.				
175	JW	45	RD and OIH	B	10/ 5/34	P.U.				
176	GM	40	ROIH	B	6/ 9/31	P.U.				
177	WM	46	RDIH	Gallie	4/ 2/32	P.U.				
178	GB	63	LOIH	B	10/22/32	Infected, healed in two months				
179	JR	44	LDIH recurrent	Gallie	12/15/33	P.U.	12/27/34	Recurrence	Swollen	
180	RE	70	LDIH	Gallie	3/22/34	P.U.				
181	FM	60	ROIH	B	8/23/34	P.U.				
182	MA	64	RDIH	Gallie	12/15/34	P.U.	12/31/34	O.K.	Swollen	
183	LB	45	LOIH recurrent	McArthur	12/21/34	Infected one month	2/ 8/35	O.K.	Normal	Testicle swollen for one month

The scrotum is elevated on a bridge for ten days. There is always considerable swelling accompanied by redness of the skin and edema of the scrotum. We must admit that in some patients, gangrene seemed imminent and actually did occur in four. The patients are kept in bed for the usual time depending on the type of hernia, and are advised to wear a suspensory until the swelling has entirely subsided, a period of from four to eight weeks.

Many of the testicles atrophy, in fact, some almost completely disappear; but it is surprising how many do not, and we frequently have to refer to our records in following our postoperative results in order to ascertain in which patients the cord has been divided.

Analysis of 200 Cases.—Complete division of the spermatic cord has been employed in the repair of 200 inguinal herniae at the Hospital for Ruptured and Crippled and Bellevue Hospital (Fourth Division). The cord was divided on one side in 166 cases, and 17 patients had hernia repair with cord division on both sides.

The youngest patient was 28 years of age and the oldest 80. The average age for the series was 54.6 years. The number of patients for each decade is shown in Table I.

TABLE I

Age

Oldest	80 years
Youngest	28 years
Average	54.6 years

Decades	*Cases*
20—29	2
30—39	12
40—49	40
50—59	67
60—69	46
70—79	15
80—	1

CASE 67.—M. M., aged 28 years, was operated upon in June, 1929, for an R.O.I.H. which recurred five months later. A Gallie fascia repair of the recurrent hernia was done on March 11, 1930, and the hernia recurred one year later. At the third operation, March 22, 1932, the sac was intimately adherent to the cord and contained adherent omentum; all landmarks were very much obliterated. The cord was divided and a Gallie fascia repair effected. Unfortunately no follow up has been secured.

The procedure was employed in all types of inguinal hernia as shown in Table II, but was particularly favored in direct or indirect recurrent types to effect a stronger repair, and in older men where it was felt that the operating time could be shortened.

Nine cases in the series are dead, six (3.2 per cent) being postoperative deaths. One case (32) died of pneumonia three and a half years after operation, one (58) died of a fractured skull following an accident 16 months after

TABLE II

	Type of Hernia				
	Simple	*Scrotal*	*Sliding*	*Irreducible*	*Recurrent*
Oblique	47 (3)*	24	12 (1)	17 (1)	25 (4)
Direct	31 (1)	3	1	1	34 (10)
Direct and oblique ...	5	—	—	—	—
Total ... 200 (20)*	83 (4)	27	13 (1)	18 (1)	59 (14)
Recurrence rate....	4.8%	0	7.7%	5.5%	23.7%

* Figures in parenthesis denote number of recurrences.

operation, and one (51) died of heart disease two years after operation. The six postoperative deaths were as follows:

CASE 3.—J. W., aged 65 years, presented a recurrent R.D. and O.I.H. with sliding cecum and the appendix in the sac. Under spinal anesthesia the appendix was removed and a Gallie fascia repair done after dividing the cord. Patient developed pneumonia and died on the third postoperative day.

CASE 26.—E. W., aged 73 years, under spinal anesthesia a ventral hernia was repaired and a Gallie fascia repair, after dividing the cord, was done for a recurrent R.D.I.H. The operating time was 40 minutes. Patient developed pneumonia and died on the third postoperative day.

CASE 44.—H. S., aged 60 years. On December 18, 1930, a Bassini type repair was done for a large R.O.I.H. irreducible, with a scrotal sac containing adherent small intestine. At operation a small hole was torn in the intestine in freeing it from the sac, the rent sutured, and the bowel reduced. Patient died on the 11th postoperative day. Autopsy disclosed a plastic peritonitis and an abscess of the abdominal wall.

CASE 90.—W. W., aged 48 years. Bassini type of repair was done on April 18, 1933, for an L.O.I.H. with a large scrotal sac. Patient died of peritonitis on the fifth postoperative day. Autopsy revealed that a portion of omentum had been tied off in the neck of the sac with the purse string suture and there was deep infection of the wound and a spread of the infection retroperitoneally.

CASE 154.—J. H., aged 74 years, presented a strangulated R.O.I.H. which was reduced after dividing the cord. A Bassini type repair was done. The wound healed by primary union but the patient developed pneumonia and died on the 20th postoperative day.

CASE 159.—M. P., aged 56 years. Gallie fascia repair of a recurrent R.D.I.H. was done on December 2, 1932. Patient developed pneumonia and died on the fourth postoperative day.

A study of the effects of the procedure on wound healing reveals that 159 wounds healed by primary union, six were drained at the lower angle at the time of operation and healed in from 10 to 30 days, while 33 wounds (17.5 per cent) became infected. In most instances the infection was of no serious consequence and responded to adequate drainage. However, one case, in which the intestine was opened at operation, developed a deep wound infection and died of peritonitis; and another case in which omentum had been ligated in the neck of the sac, developed a deep wound abscess and died of peritonitis. However, in four cases late infection set in from the sixth to the 35th day due to a necrosis of the testicle, necessitating orchidectomy. It may

be noted that none of these four cases showed a recurrence of the hernia when last examined.

CASE 102.—S. G., aged 50 years, had a Gallie fascia repair of a recurrent R.O.I.H. The wound was opened widely on the sixth day because of extensive suppuration. The infection spread, involving the distal segment of the cord and testicle so that an orchidectomy was done on the 13th day. Recovery was prompt, and 15 months later the hernia repair was found to be solid.

CASE 142.—J. M., aged 61 years, presented a large irreducible scrotal L.O.I.H. for which a Gallie fascia repair was done after dividing the cord to facilitate a repair. The scrotum became quite swollen and was drained on the 17th postoperative day. It was soon apparent that the testicle was necrotic, and four days later orchidectomy was done followed by prompt healing of the wound. There was no recurrence of the hernia when the patient was examined 20 months later.

CASE 169.—C. E., aged 70 years. This patient, who was very obese, was admitted with a large scrotal hernia on the right side which had recently become incarcerated, and a large scrotal hernia on the left which had been irreducible for several years. Operation was done under spinal anesthesia and the right cord divided to facilitate repair. No attempt was made to repair the left side. The scrotum was moderately swollen after the operation but not until the fifth week was fluctuation elicited and the scrotum drained and the testicle removed. Wound healing was slow but was complete 12 weeks after the original operation. Patient was examined 17 months later and there was no evidence of recurrence. The unoperated left hernia gave him no trouble.

CASE 173.—J. B., aged 41 years. Bassini type repair of an R.O.I.H. On the seventh day there was evidence of wound infection, which spread into the scrotum and involved the testicle; orchidectomy was done 18 days after operation, followed by prompt wound healing in one week. Six months later, patient was examined and the wounds were healed; there was no evidence of a recurrence of the hernia.

One other case remained free of infection but developed a large hydrocele. It was considered advisable, in view of the already damaged blood supply and the fact that a typical hydrocele operation would interfere with the collateral circulation, to remove the testicle with the hydrocele sac five months after the hernia repair.

CASE 116.—L. C., aged 60 years. Patient had a L.O.I.H. and a Bassini type repair was done with division of the cord on the left side only. The wounds healed by primary union but the patient developed a large hydrocele because the scrotal part of the sac had not been removed. This was removed at operation five months later, and the testicle, although normal in size and appearance, was removed because of its close relation to the hydrocele.

Although 169 cases returned to the clinic and the condition of the hernia wound was noted, only 79 follow up notes report the condition of the testicle. A fairly common observation was moderate swelling of the testicle for one or two months after operation followed by diminution in the swelling to normal or going on to atrophy. One testicle remained swollen for six months and another for one year. We believe it fair to assume that if marked atrophy had occurred in those patients in which the condition of the testicle was not noted, the majority of them would have noticed it themselves and called our attention to the fact. The testicle was recorded normal in size in 42 instances (25 of which were followed from one to five years). Incidentally, all cases

subjected to bilateral division of the cord were found—where mention was made of the condition of the testicle—to have normal size testicles on both sides. Eleven cases showed slight atrophy, and 11 others showed atrophy to one-half or less of the normal size.

An analysis of the follow up records reveals that 31 cases were not traced after they left the hospital. Of the 169 that returned for one or more examinations, 20 (11.8 per cent of the followed cases) were found to have a recurrence of their hernia. One case recurred as early as one month after operation, and one as late as 39 months, with an average interval of 9.5 months from operation to recurrence. As might be expected, the highest recurrence rate (14 recurrences out of 59 operations occurred in those cases that were operated on for a once, or twice recurrent hernia. The number of recurrences for the different types of hernia is shown in Table II; and Table III shows the rate of recurrence for the different types of operation.

TABLE III

Percentage of Recurrences

Type of Operation	No. of Cases	No. of Recurrences
Bassini	80	4 or 5.%
Gallie	87	10 or 11.5%
Ox fascia	25	5 or 20.0%
Hotchkiss	5	1 or 20 0%
Wyllys Andrews	2	—
McArthur	1	—
	200	20 or 10.0%

Analyzing the death rate: There were four deaths (the patients were between 60 and 80 years) in 62 operations, a mortality of 6.5 per cent. Three of the deaths were from pneumonia. This was before we were using CO_2 and oxygen as a routine after all spinal anesthesias. It is quite possible that its use might have prevented some of them. The deaths from peritonitis were distinct technical errors on our part.

These patients have been operated on by a fairly large group of surgeons in each hospital, and we are all impressed with: first, the value of cord division in diminishing the operating time in elderly people; and second, the efficiency in insuring a more perfect repair in sliding hernia and in many types of recurrent hernia.

COMMENT.—One hundred and nineteen of the 182 cases occurred in the fifth, sixth, seventh and eighth decades, the fifth predominating. Nearly all the younger patients had cord division for recurrences. The recurrence rate for the latter group is high, 23.7 per cent, but we believe we have obtained better results than we would have without division of the cord. In the non-recurrent cases our percentage of failures is distinctly lower than we would have had without division of the cord. This applies especially to the sliding types with a recurrence rate of 7.7 per cent.

TABLE IV

Percentage of Infections

Type of Operation	No. of Cases	No. of Infections
Bassini	80	11 or 13.7%
Gallie	87	11 or 12.6%
Ox fascia	25	10 or 40.0%
Hotchkiss	5	—
Wyllys Andrews	2	—
McArthur	1	1 or 100%
	200	33 or 17.0%

The infection rate is lamentably high (Table IV). An infected vas deferens might explain some of these; and in a certain number of cases we have cauterized the stumps but not in a sufficient number to ascertain whether this had any definite bearing. Forty per cent of the cases in which ox fascia was used became infected, and this suture material has been discarded. Eliminating this group and also the four cases in which the testicles sloughed, plus the two with sloughing of the lower end of the hernial sac, leaves 17 infections in 169 operations, a percentage of 10 per cent. This corresponds very closely to the results obtained in the Gallie repair without division of the cord. Two patients later developed infections, one in the inguinal wound, and the other, a sinus in the scrotum. We assumed the testicle was sloughing in each instance but on incising the scrotum a slough of the lower end of the hernial sac was found. The wounds healed promptly after its removal and the testicles were not involved.

THE UNDESCENDED TESTIS

ITS FATE AFTER SATISFACTORY SCROTAL ANCHORAGE

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JOHN HUNTER[11] believed that the undescended testis failed to reach the scrotum because of inherent imperfection. With the advent of aseptic surgery, operative procedures have been developed which will permit of satisfactory scrotal anchorage of the incompletely descended testis in the majority of instances. Though the deformity may be corrected by surgery and a good cosmetic result obtained, considerable doubt still persists in the minds of most medical men concerning the functional worth of scrotal transference of the undescended testis.

That the imperfectly descended testis is aspermatic has long been known. The cause for its inability to develop complete spermatogenesis has been the subject of considerable speculation and experimentation. Piana[18] and Crew[5a] have each suggested that the higher body temperature is unfavorable for the elaboration of mature germinal epithelium in a retained testis. The researches of Moore[17] and Fukui[8] gave complete support to this hypothesis. Moore's suggestion that the scrotum is a temperature regulating mechanism appears to be well established for the normal testis, for after elevation of the completely descended testis to the abdomen, upon its return to the scrotum, there is restoration of normal spermatogenesis (Fig. 1).

Many, including the writer,[23] have inferred that the undescended testis would develop normally when afforded the advantages which the scrotum accords the testis which descends in the normal manner. No proof, however, has yet been adduced to indicate whether this surmise is correct or not. That rationalization may frequently lead to error is a matter of general knowledge, even though not sufficiently appreciated. Speculation as to the verity of a conclusion reached by a process of rationalization can be done away with only when the subject under discussion has been subjected to the acid test of direct experiment.

Histology of the Retained Testis.—The writer[23] has elsewhere summarized at some length certain facts concerning the gross and microscopic anatomy of the testes which relate to the aspermatic condition of the undescended testis. Briefly it may be said that the normal testis grows but slightly from birth to puberty, and similarly, during this interval of time there are very few histologic changes. The undescended testis before puberty resembles its fellow in the scrotum in both matters of weight and minute anatomy. With the onset of puberty, however, the normal testis shows a sharp increase in weight accounted for by the elaboration of a mature germinal epithelium and the ap-

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pearance of spermatozoa. The undescended testis similarly exhibits these changes but in lesser degree. In the retained testes of children just past

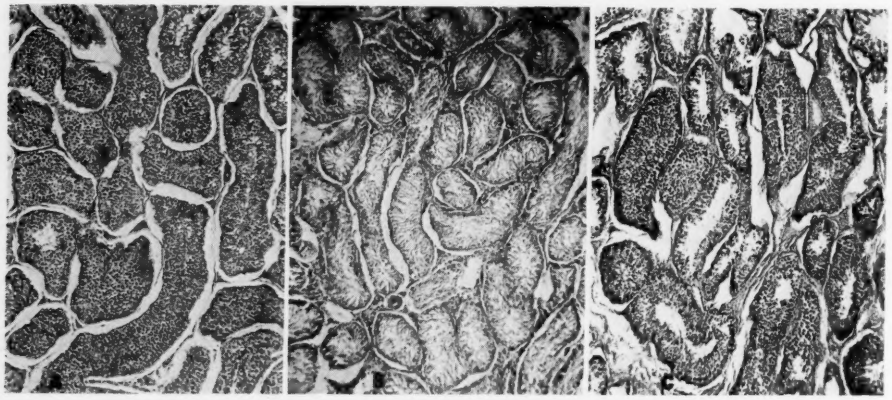

FIG. 1.—(A) Section from the normal testis of an adult dog. (B) The same testis after having been in the abdomen 37 days. (C) The other scrotal testis of the same dog 190 days after scrotal replacement; it was also in the abdomen for 37 days. No change attends the elevation of the prepuberty dog's testis to the abdomen.

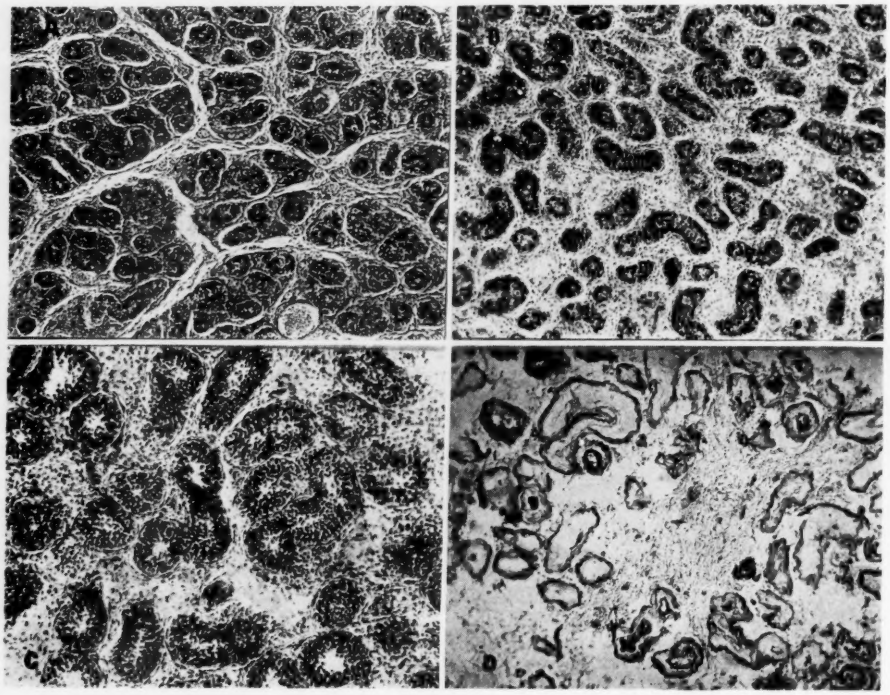

FIG. 2.—(A) Section from abdominal testis of a seven months old premature. (B) Scrotal testis of an 11 year old child. (C) Undescended testis of a 13 year old boy. Spermatozoa are not apparent in the section, but a fairly mature germinal epithelium is present. (D) Undescended testis of a 56 year old man.

puberty spermatogonia may be demonstrated in the seminiferous tubules in abundance, but spermatozoa in my experience have not been observed. With increasing years the germinal epithelium becomes more and more atrophic,

such that in retained testes removed past the meridian of life, only the outlines of the seminiferous tubules occasionally persist (Fig. 2 D).

The occurrence of spermatozoa in retained testes in the young has been described, but their presence is decidedly unusual. An active spermatogenesis is probably never maintained. It would appear that inasmuch as the operation of orchiopexy has been practised for more than 50 years, information should be readily accessible as to what scrotal transference profits the incompletely descended testis. Even when acknowledgment is made of the admitted difficulties surrounding the problem of obtaining satisfactory examinations during life, it is astonishing how little information is available with reference to this important question. A few isolated instances where spermatozoa have been observed in the semen of patients after bilateral orchiopexy have been reported. No mention of this significant item has come to the writer's attention in the literature of the last fifteen years.* Reports after orchiopexy have been concerned largely with the size, position, and general cosmetic result of the operation.

Purpose and Method.—The purpose of this paper is to set forth the results of scrotal transference of the undescended testis as it relates to the question of spermatogenesis. Nine years ago the writer first employed and later described a method of obtaining satisfactory scrotal anchorage of the undescended testis (Fig. 10). Three years ago it was appreciated that this method of orchiopexy permitted determination of the influence of the scrotal position upon the histology of the undescended testis. A small piece of testicular tissue was removed for histologic examination at the time of the initial operation, and again later when the cutaneous union between the thigh and scrotum was undone. Similar observations have also been made upon a bull, several pigs, and dogs with incomplete testicular descent. Semen examinations have been possible in some of the cases of human cryptorchidism after bilateral orchiopexy.

Results.—In 1931 through the courtesy of Drs. C. P. Fitch and W. L. Boyd, Professors of Veterinary Medicine at the University of Minnesota, it was my privilege to operate upon a young Holstein bull six months old, of valuable pedigree, for bilateral cryptorchidism. My colleague, Dr. M. H. Manson, assisted with the operation.

Satisfactory anesthesia was obtained by the intraspinal injection of 150 mg. of novocaine. The bull's hind quarters in a few minutes failed to support him and he was fastened in the dorsal decubitus position. After preparation of the abdomen by clipping the hair with shears, iodine was applied and an aseptic laparotomy was performed. Both testes were found within the peritoneal cavity. There was considerable torsion of the left spermatic cord without infarction of the testis. The testis could not be adequately mobilized to bring it outside the abdomen and consequently it was excised. The right

* A very interesting discussion of the subject has just appeared under the title of "Clinical Study of the Spermatogenesis of Undescended Testes," by D. W. MacCollum of Boston, in the Arch. of Surgery, vol. 31, p. 290, August, 1935.

testis, on the contrary, was brought into the scrotal pocket with relative ease after division of some of the avascular bands of connective tissue surrounding the spermatic vessels. A heavy, double, silk suture secured to the tunica albuginea was brought through the skin of the scrotum and tied over a small gauze dressing to maintain the testis in as favorable a position as possible.

The bull made an uneventful convalescence and the immediate result was all that could be desired. With the elapse of time, however, the testis retracted to the upper portion of the scrotum, a behavior well known in human cases after the Schüller-Bevan[19, 2] type of orchiopexy (Fig. 3).

On January 29, 1932, Professor Boyd wrote me the following comprehensive note concerning the subsequent status of the bull. "I wish to report that the young Holstein sire on which you performed orchiopexy during

FIG. 3.—(A and B) Photographs of bull, made about nine months after right orchiopexy. The testis is small and has retracted into a high scrotal position.

February, 1931, made a complete recovery without any suppuration. After he had fully recovered he was shipped home. During the month of June he was permitted to serve three virgin heifers, two of which failed to again come in estrum. The third appeared in estrum at the regular period and was served by another sire. The two in which there was a cessation of estrum were thought to be in calf and were cared for as such. The bull developed into an average sized animal for his age and though he developed a good crest and other male characteristics, his conformation proved a disappointment to the owner and he was not again placed in service. During the early part of December, 1931, I conducted a careful physical examination of this bull and found his testis, which was situated in the upper region of the scrotum, to be very small, more or less flattened, and adherent to its covering. I massaged his seminal glands and the discharge collected at the opening of the sheath failed to show the presence of spermatozoa. I then examined the heifers supposedly in calf and found them open or not pregnant. The cessation of

estrum in each instance was the result of a retained corpus luteum. We then permitted the bull to serve a cow which he did in a very rapid and vigorous manner. The discharge from this service which was largely water-like was carefully examined for the presence of spermatozoa and found negative. The superintendent then decided it was wise to castrate this animal to which I consented.

"I spoke of securing the testis for histologic studies but apparently failed to impress them with this request. I wrote to the veterinarian upon arriving home, and during our meeting in early January I was informed that the animal had been castrated and that the testis was probably lost. I believe that we can safely consider that the animal in question developed in a very masculine way just as any normal sire would do, but I do not believe that spermatogenesis ever took place."

In 1932 I brought the testes of a dog, with bilateral failure of testicular descent, into the scrotum, and my associate, Dr. Charles Rea, has recently done a similar procedure on three dogs with unilateral failure of descent. Subsequent biopsies of the testes failed to show a mature germinal epithelium but as yet smears from the cut surface of the testis and from the seminal vesicles have not been made nor has the semen been examined for spermatozoa. One of the likely hindrances to a satisfactory result is the difficulty of getting the testis well down in the scrotum and keeping it there.

With the future cooperation of Professor Fitch it was possible to secure several young pigs with unilateral or bilateral failure of testicular descent through the courtesy of several veterinary surgeons in the environs of Minneapolis. A few additional pigs were also obtained at the stockyards in South St. Paul with the coöperation of Mr. Ralph Lewis.

In all, 15 pigs were brought to the laboratory of experimental surgery for the purposes of this study. Several were found unsuitable because both testes had been previously removed, or the supposedly retained testis was absent. Three of the group presented inguinal retention of the testis and in each instance the testis was readily brought into the scrotum. The results of these experiments are summarized in Table I. The writer here gratefully acknowledges the help of his associate, Dr. Louis Sperling, in the operative procedures, who at the time was occupied in the laboratory with experimental features of bowel obstruction.

COMMENT

It is apparent from these observations that scrotal transference has a favorable influence on the undescended testis. In the three pigs with inguinal retention of the testis, adult germinal epithelium developed in each instance after orchiopexy. In one, the final size of the transplanted testis (Fig. 4, Table I) together with the presence of a mature spermatogenesis in all the seminiferous tubules attested the restoration of the normal condition (Fig. 4). In the other two, in which the scrotal anchorage, as far as could be determined, was just as satisfactory, a normal adult spermatogenesis was apparent only here and there in the sections. Nevertheless, when these sections are contrasted with the histologic picture presented by retained testes of adult pigs or

TABLE I

RESULTS OF ORCHIOPEXY ON PIGS FOR UNDESCENDED TESTIS

No.	Age	Weight (lbs.)	Date of Operation	Position of Testis	Procedure	Histologic Findings at Time of Operation	Subsequent Findings and Final Status of Testis
1	Adult	200	2/6/32	Left descended; right previously removed	Excision of left testis	Left normal	Weight of removed testis and epididymis, 360 Gm.
2	Adolescent		2/13/32	Left scrotal; right inguinal	Biopsy both; orchiopexy of right	Both prepuberty	12/7/32 pig killed. Weight of left testis, 392 Gm.; weight of right, 135 Gm.; surrounded by dense connective tissue; scattered islands of normal spermatogenesis with spermatozoa
3	Adult	186	2/13/32	Both intraperitoneal	Both excised	Both atrophic and aspermatic	Weight of right, 120 Gm.; weight of left, 116 Gm.
4	4 wks.	14	2/22/32	Right scrotal; left inguinal	Bilateral biopsy and left orchiopexy	Both prepuberty	Killed 4/22/33. 6.5 × 12 × 6 cm. Both equal size; mature germinal epithelium with myriads of spermatozoa in each testis
5	Adolescent	50	2/22/32	Right scrotal with hernia; left inguinal testis with small hernia	Repair of right hernia; repair of left hernia and orchiopexy	Both prepuberty	Killed 6/30/32. Granulomatous tumor about right testis. Weight of left, 199 Gm.; mature germinal epithelium with scattered spermatozoa
6	Adolescent	90	3/5/32	Right scrotal; left absent			
7	Adult	180	3/5/32	Right scrotal; left abdominal	Both excised; left could not be brought into scrotum	Right normal; left atrophic	Weight of right testis, 400 Gm.; weight of left testis, 70 Gm.

8	Adult	220	3/5/32	Right apparently previously removed; left scrotal	Left excised	Left normal	Weight of left testis and epididymis, 450 Gm.
9	Adolescent	40	5/9/32	Both intraperitoneal	Biopsy both testes; right left in abdomen; left anchored beneath skin of groin	Both prepuberty	Six weeks after operation developed hernia and granulomatous mass about left transplanted testis. Killed 7/20/32
10	6 wks.	28	6/30/32	Right previously removed; left intraperitoneal	Anchorage of left testis beneath skin of groin	Prepuberty testis	Died bronchopneumonia 7/6/32. Weight of right testis 18.8 Gm.; weight of left testis 18.8 Gm.
11	5 wks.	27	6/30/32	Right intraperitoneal; left previously removed	Anchorage beneath skin of groin	Prepuberty testis	Initial measurements of right testis—$1\frac{1}{4} \times 27/32 \times 15/16$ inches. Pig killed 11/26/32. Measurements—$2\frac{3}{8} \times 1\frac{5}{16} \times 1\frac{5}{16}$ inches. Atrophic histologically
12	3 mos.	62	6/30/32	Right previously removed; left intraperitoneal	Anchorage of left testis in groin	Prepuberty testis	Died of peritonitis 7/4/32
13	3 mos.	62	7/2/32	Both testes previously removed	Exploratory		
14	4 wks.	25	7/2/32	Right absent; left intraperitoneal	Biopsy and anchorage of left testis in groin	Prepuberty testis	Killed 4/22/33. Initial measurements—$1\frac{3}{8} \times 1 \times \frac{31}{32}$ inches. Final measurements—$1\frac{3}{4} \times 1\frac{3}{8} \times 1\frac{3}{8}$. Atrophic histologically.
15	5 wks.	20	7/19/32	Right scrotal; left intraperitoneal	Biopsy of both; anchorage of left in groin	Prepuberty testis	Killed 11/26/32. Measurements of right scrotal testis—$2\frac{3}{8} \times 1\frac{5}{16} \times 1\frac{1}{2}$ inches; histologically normal. Left testis involved in large granulomatous mass.

that of abdominally retained testes anchored beneath the skin of the groin, it is obvious that the germinal epithelium is improved by scrotal transference (Figs. 4 and 5).

Results after Orchiopexy in Man.—In the human cases, as has been stated, an opportunity was afforded to remove a small piece of tissue for biopsy at

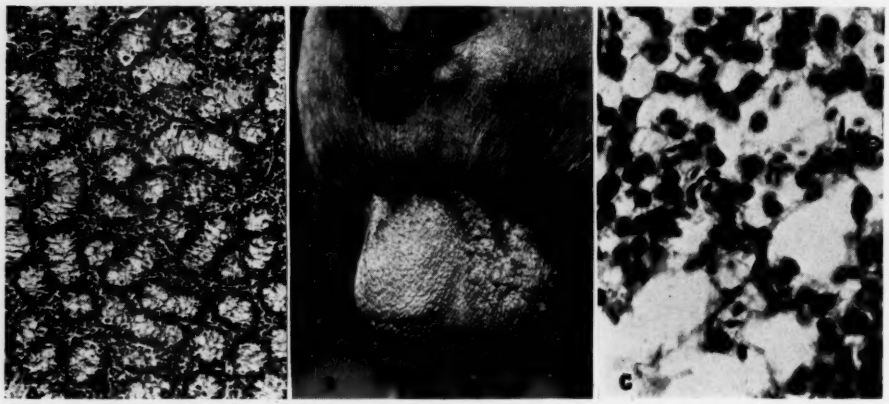

FIG. 4.—(A) Inguinal testis of a four weeks old pig. The histology of the scrotal and the retained testis was quite the same (prepuberty testis). (B) Photograph several months later. Both testis exhibit considerable growth (Pig 2, Table I). (C) Section of retained testis 14 months after orchiopexy. A complete spermatogenesis is present.

the time that the cutaneous union between scrotum and thigh was undone, the testis meanwhile having been in the scrotum for several months. By and large, the results of these microscopic examinations were somewhat disappointing. Though the state of the germinal epithelium, on the whole, ex-

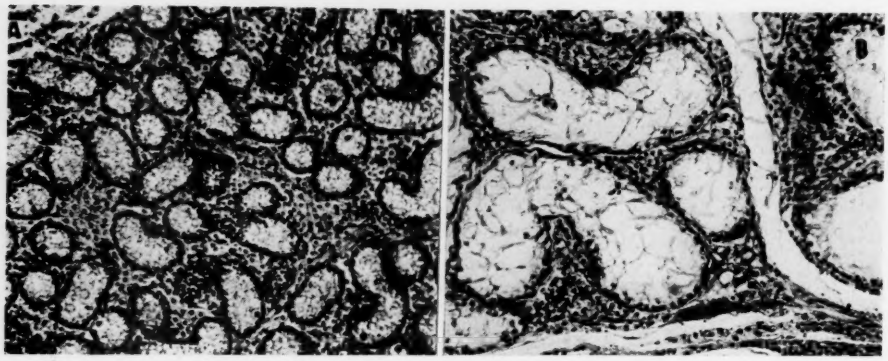

FIG. 5.—(A) Section of prepuberty abdominal testis of pig (Pig 11, Table I). (B) Same testis, five months after anchorage beneath the skin of the groin. There is no evidence of a mature germinal epithelium.

hibited distinct improvement over that observed initially, nevertheless the normal adult state was never attained. Yet, in the only instance in which the testis* has been available for examination at a date remote from the per-

* This boy (see Table II, Case 3) was killed in a motorcycle accident sixteen months after the last scrotal detachment. Through the cooperation of Dr. George R. Dunn of Minneapolis, and the kindly attitude of the father, permission was obtained to secure the testes for histologic examination. (See Fig. 6.)

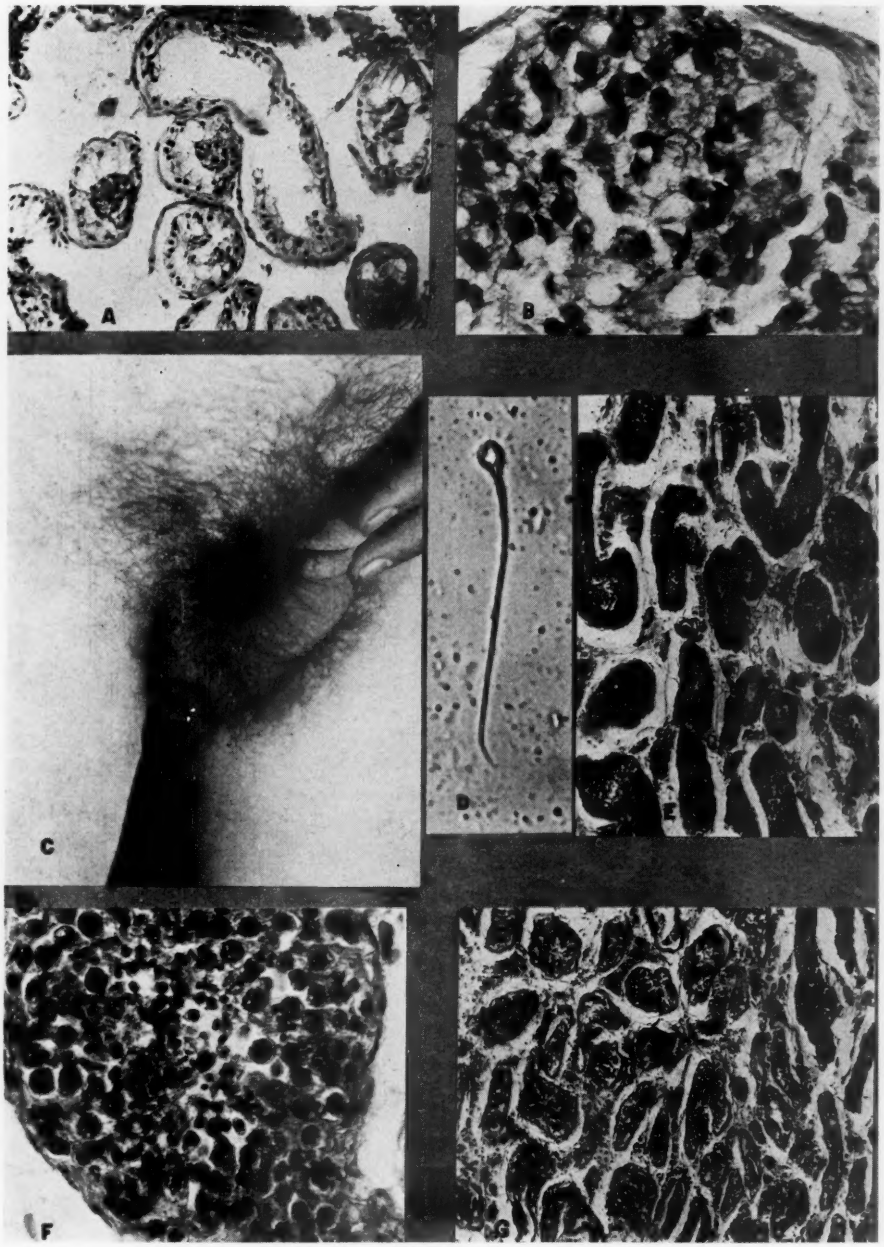

FIG. 6.—(A) Section of retained testis (right) of a boy of 20, obtained at the time of operation (×180). (B) Section of same testis six months after scrotal anchorage (×700). (C) Photograph after bilateral orchiopexy. (D) Photograph of a spermatozoon (×1000). (E) Section of right testis obtained at necropsy (×180). (F) Section indicating the presence of spermatozoa (×700). The condition shown in (E) was present throughout the greater portion of the testis. (G) Section of an area in same testis indicating atrophic tubules (×180).

TABLE II

EXAMINATION OF SEMEN IN BILATERAL AND UNILATERAL CASES BEFORE AND AFTER ORCHIOPEXY

No.	Hospital Number	Side	Preoperative Position of Testis	Semen Examination before Operation	Present Age	Age at Time of Orchiopexy	Date and Nature of Operation*	Cosmetic Result, Position and Size of Testis†	Functional Result: Semen Examination, Amount and Number of Sperm Cells
1	593975 (W.N.)	Bilateral	Both inguinal	Not done	17	11	3/29/30 right orchiopexy 6/30/30 right detached and left orchiopexy	E—⅔ adult size 4/8/35 left detached and biopsy of both	5/1/35. 7 cc. 3–4 sperm per high power field
2	593497 (P.U.)	Bilateral	Both inguinal	Not done	19	14	6/18/30 bilateral orchiopexy 12/27/30 bilateral detachment	E—testis small ½ normal	5/17/35. 1 cc. Sperm present but scarce
3	617782 (R.N.)	Bilateral	Both inguinal	Not done	23	20	6/13/33 right orchiopexy 8/23/33 right detached and left orchiopexy. 12/22/33 biopsy of both	E—⅔ adult size	4/25/35. 3 cc. Sperm present (Fig. 6, E)
4	591998 (G.M.)	Bilateral	Both inguinal	Not done	34	29	2/1/30 bilateral orchiopexy 9/5/30 right excised	E—⅔ adult size	5/23/35. 1.5 cc. No sperm cells found
5	58386 (A.K.)	Bilateral	Both inguinal	Not done	19	15	3/23/31 right orchiopexy; left not done yet	E—about adult size	5/22/35. 3 cc. 900 sperm per cu. Mm., *i.e.*, 2,700,000 in specimen
6	62961 (J.M.)	Bilateral	Both inguinal	Not done	21	18	3/7/32 right excised because of tortion; left orchiopexy	E—⅔ adult size	5/22/35. Two examinations; none found. This patient had a group of many deep furuncles over the skin of the

										lower back and sacrum at the time of examination.
7	40875 (S.L.)	Bilateral	Both intra-abdominal	Not done		24	16	7/29/27 bilateral orchiopexy	E—⅔ adult size	Not done yet
8	626378 (V.H.)	Bilateral	Left inguinal, right intra-abdominal	Not done		19	19	5/3/35 right orchiopexy	Still attached	Not examined since operation
9	634558 (O.B.)	Bilateral	Both inguinal	Not done		20	20	5/22/35 right orchiopexy	Still attached	Not examined since operation
10	47368 (S.S.)	Left side	Inguinal	Not done		27	20	2/21/29 left orchiopexy 5/28/29 detachment	E—⅔ size of scrotal testis	5/15/35. 2 cc. 39,000 per cu. Mm., *i.e.*, 78,000,000 in specimen
11	624110 (E.R.)	Left side	Left inguinal, right scrotal	Not done		27	26	3/3/34 left orchiopexy	E—⅔ size of scrotal testis	5/15/35. 10 cc. 46,000 per cu. Mm., *i.e.*, 460,000,000 in specimen
12	630358 (G.G.)	Right side	Right inguinal; left scrotal	Not done		24	23	11/12/34 right orchiopexy 4/23/35 detachment	E—both testes the same size	5/28/35. 3 cc. No sperm cells found
13	628680 (H.G.)	Left side	Left inguinal, right scrotal with hernia	Not done		25	24	6/21/34 left orchiopexy 4/25/35 detachment and biopsy of both testes	E—both testis the same size	4/25/35. 3 cc. None 5/20/35. 3 cc. None
14	47959 (L.K.)	Right side	Right inguinal; varicocele in left spermatic cord	Not done		21	15	4/8/29 right orchiopexy and repair of left varicocele	E—testis small ½ normal	5/28/35. 3 cc. 160 per cu. Mm., *i.e.*, 480,000 in specimen

* The orchiopexy described by the author was used in all these cases.

† For purposes of brief tabulation, results with reference to position of the testis are designated as E—excellent; G—good; F—fair; and P—poor. Almost invariably a mobile testis at the bottom of the scrotum was found.

formance of the orchiopexy, an histologic picture not unlike the normal was found throughout the greater portion of the right testis;* and in the left, isolated areas with a mature spermatogenesis were present throughout, though the tubules presenting an atrophic epithelium outnumbered the normal considerably. Even in the right testis there were scattered areas in which the seminiferous tubules were devoid of germinal cells (Fig. 6).

It is eminently significant that out of six cases presenting bilateral failure of descent, after orchiopexy spermatozoa were demonstrated in the semen in four. In the two in which sperm failed of demonstration, the testis† in each instance was of good size (though probably slightly smaller than the average adult normal testis) and freely mobile in the scrotum. In one of these, orchiopexy was performed at the age of 29. When one bears in mind the usual histologic picture of the undescended testis for this age, it is not surprising that scrotal transference at such a late date did not permit of the demonstration of spermatozoa in the semen. In the instance of the other, he was suffering from a fascial plane suppuration originating in a severe furunculosis of the lower back at the time of the semen examination. The unfavorable effect of illness upon spermatogenesis has been elsewhere pointed out.[23]

It is particularly noteworthy that in the two patients with bilateral failure of descent in which semen examinations were done *before* operation, no spermatozoa were found. Unilateral orchiopexy has been done too recently in these cases to note the effect of scrotal transference of the testis upon the cytology of the semen.

When one compares the results of the semen examinations‡ in the unilateral cases with those observed in patients presenting bilateral failure of testicular descent, the contrast is striking. Whereas, in the unilateral cases, a swarm of motile cells may usually be seen in any field, one not infrequently must search the preparation diligently to demonstrate the presence of spermatozoa in the bilateral cases. In the unilateral cases 10 and 11 (Table II) 39,000 and 46,000 sperm were demonstrated per cc. of spermatic fluid. The aggregate sperm count for the specimen¶ in each instance was respectively

* The greater elapse of time since orchiopexy was done is undoubtedly a prominent factor in the greatly improved character of the germinal epithelium over that obtained by biopsy sixteen months before. Yet the semen examination which revealed only occasional spermatozoa was done only about a week before death.

† Sacrifice of the right testis in the instance of the 29 year old man (Table II, Case 4) was done by choice; in the case of J. M., aged 18 (Case 6) a left sided orchiopexy was done at the same time that a right retained testis was excised because of torsion of the cord and infarction of the testis.

‡ Failure to demonstrate spermatozoa in the instance of the two unilateral cases (12 and 13) is quite understandable for in each instance a biopsy had been made on each testis with the patient's consent at the time of the unilateral scrotal detachment about ten days before the semen examinations were made. The writer has previously called attention to the temporary unfavorable effect upon the histology of the testis of operative manipulation of either testis or spermatic cord.[23]

¶ Ejaculated specimens; semen examinations on fluid obtained as a result of prostatic massage are particularly untrustworthy, sperm not infrequently being absent in the secretion of ward patients with scrotal testes.

78,000,000 and 460,000,000. A dilution of one to ten with saline was made in a white blood cell counting pipette and several counts were made from each specimen in a regular blood cell counting chamber, after movement in the preparation had ceased (Fig. 7, A and B).*

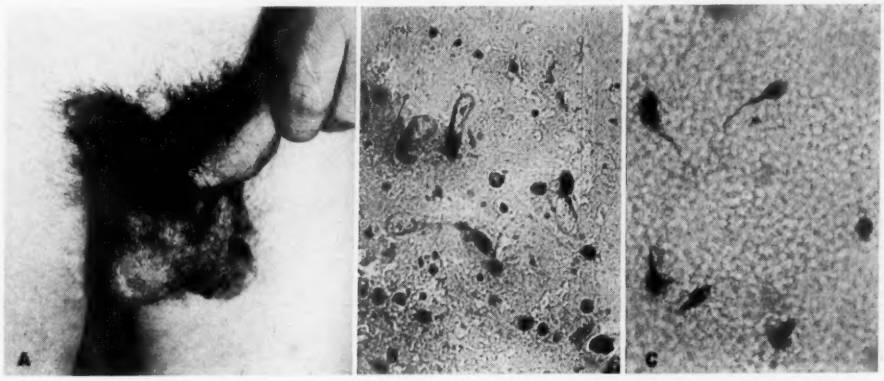

FIG. 7—(A) Condition after bilateral orchiopexy in Case I. The photographs made at intermediate stages of the operative procedure are shown in Fig. 13, Surg., Gynec., and Obst., vol. 54, p. 219, 1932. (B) Iron hematoxylin stain of a smear of the semen; several spermatozoa can be seen in every field (×700). A cell count was not done, but sperm did not appear as numerous as in Fig. 7,C in the fresh preparation. (C) The same preparation in a unilateral case after orchiopexy (×700). (Case 11, Table II. There were 46,000 sperms per cm.

The writer has examined histologically a large number of undescended testes from the dog, pig, horse, and man. In no instance has a mature spermatogenesis been observed.† In retained testes which are just past puberty,

FIG. 8.—(A) The section of a retained testis of an adult pig. (B) Smear from one of the seminal vesicles showing spermatozoa (sperm have also been found on smear of the cut surface of the testis and from the seminal vesicle in an adult pig with bilateral abdominal testes.) It is interesting to see that such a poor germinal epithelium may elaborate spermatozoa.

spermatogonia and spermatocytes can usually be found in large numbers in most of the tubules (Fig. 2, C). With increasing age, these disappear and

* Mrs. Gleva L. Erskine, Medical Technician, kindly made these counts for me and with the help of Mrs. Anna L. Johnson of the laboratory of neuropathology, prepared the sections shown in Fig. 7, B and C.

† The abdominal testes of four horses were made available to me through the courtesy of Doctor Boyd. Though no spermatozoa were found (smears not made) it is my impression that the germinal epithelium of the horse is far better maintained in a retained testis than that of man, pig, dog, or bull.

eventually only the outlines of the tubules with a few Sertoli cells and spermatogonia persist. With the experience in mind of being able to demonstrate spermatozoa in the semen when the tissue removed from the testis (at the time that the scrotal attachment was undone following bilateral orchiopexy) failed to exhibit complete spermatogenesis, observations have been made on pigs with undescended testis at the Armour packing plant in South St. Paul.* Tissues were excised from the following organs in pigs with undescended testes: testis, epididymis, seminal vesicle, prostate, and the bulbo-urethral gland. At the same time, smears were made from the cut surface of testis, epididymis, and seminal vesicle, and after staining, these sections were studied for spermatozoa. These observations will be later published in more detail together with my associates, Drs. George Bergh and Charles Rea. Suffice it here to say that we frequently were able to demonstrate spermatozoa in a smear made from the cut surface of the testis and from the interior of the seminal vesicle, when a study of the histologic sections of the testis revealed a very atrophic germinal epithelium (Fig. 8).† Similar studies on the semen in bilateral unoperated human cryptorchids will probably also occasionally reveal the presence of spermatozoa. I am inclined to believe, therefore, that whereas such cryptorchids are usually sterile, they may occasionally be potentially fecund in the early years after puberty.

However, the improvement afforded the germinal epithelium of the undescended testis by scrotal transference attests the virtue of orchiopexy. An undescended testis properly anchored in the scrotum before atrophy of the germinal epithelium has occurred, is, as has been indicated, capable of a mature spermatogenesis.

Cause of Lack of Uniform Restoration of Germinal Epithelium after Orchiopexy.—Just why such a testis does not produce spermatozoa with the same profusion as the normal is not apparent. The normal testis of the dog elevated to the peritoneal cavity and later returned to the scrotum reproduces again a quite normal germinal epithelium.

Before demonstrating the presence of spermatozoa in the semen of cryptorchids after bilateral orchiopexy, I was inclined to blame the abnormal separation of vas deferens and testis, believing that this anomaly might be associated with obstructions in the epididymis or efferent ductules. This finding is a frequent occurrence in undescended testes (Fig. 9). On three occasions when operating for failure of testicular descent, I have not been able to demonstrate the presence of a testis after carrying the search well into the retroperitoneal region, though a vas deferens in each instance was readily found. It has been adequately shown that ligature of the vas deferens does not cause atrophy of the germinal epithelium. Still, ligation of the excretory ducts of

* Through the courtesy and cooperation of Mr. H. L. Wilkinson, Assistant Manager, and Drs. Thomas and Earl Lowe, physicians to the plant.

† These observations clearly indicate that smears of the cut surface of the testis and from the seminal vesicle are a far more reliable index of the absence or presence of spermatozoa than a study of an histologic section of the testis.

other glands such as the liver, pancreas, kidney, or salivary gland is invariably accompanied by profound histologic changes. I rather felt that this difference in behavior was due to the intervening long coiled tubular duct, the epididymis. Every gland with an excretory duct has a certain secretory pressure. Should the epididymis act as a buffer, one ought to find very low pressures in the vas deferens. Recently my associate, Dr. John R. Paine, and I have measured these pressures in patients having division of the vas deferens before transurethral resection of the prostate. Low pressures were invariably found. (Results of this study will be published elsewhere.)

FIG. 9.—Photograph showing separation of epididymis from the testis in the retained testis of a pig. A similar separation of testes and epididymis is found frequently in human cases, though usually less marked than shown here.

The demonstration of spermatozoa in the semen of cryptorchids effectually puts aside the premise that obstructions are present in the duct system. The suggestion that it may be a hormonal influence upon the germinal epithelium appears to be adequately set aside in the normal condition of the scrotal testis in unilateral cases. The contention of John Hunter that the germinal epithelium of the undescended testis possesses inherent diminished potentialities cannot be gainsaid, but certainly the epithelium of such a testis after scrotal fixation exhibits regenerative properties within certain limits.

That satisfactory scrotal fixation is an important determinant has long been apparent in the size of the testis as correlated with its scrotal position. With the comparative sperm counts in mind observed in unilateral and bilateral cases after orchiopexy, it would appear that some factor other than technical considerations affect the issue. Nevertheless, a good scrotal anchorage performed at the optimal time (just before puberty) and without blood vessel damage affords the undescended testis the greatest promise.

As the years go by, and some of the patients with bilateral failure of testicular descent for whom I have performed bilateral orchiopexy marry, an opportunity will be afforded to note the extent of their potential fertility. Certainly it would appear that paternity is possible in such a patient as A. K. (Case 5, Table II), who has 900,000 sperms per Cm. of semen with only one testis brought into the scrotum. When one contemplates the lavish prodigality with which the reproductive capacities of the normal male are endowed, he must feel stirred by a profound and unfathomable wonder concerning the reasons which prompted nature in this profligate provision.

Practical Considerations.—The results of this study indicate that orchiopexy when well performed is not alone a cosmetic procedure but a functional operation as well, in that it accords the retained testis the most favorable advantage possible for normal development. In bilateral failure of descent (20 per cent of the cases in my experience), the need for the operation may be readily appreciated. The best time for the operation is just before puberty. Inasmuch as pubescent changes become apparent in most boys between 12 and 13 years, the necessary operative procedures, by election, should be done so that the testes will be in the scrotum when the testicular changes incident to puberty occur.*

The operation might well be deferred until 9 to 11 years of age unless an associated hernia or pain prompts its earlier performance. As has been pointed out previously, the testis grows but slightly if at all from birth to puberty. Similarly, the histology of the newborn's testis and that of the child of 11 years, whether the testis be scrotal or retained, are quite identical, and occasionally a testis will descend spontaneously. The frequency of this occurrence, however, cannot be as great as my medical colleague Dr. Drake[6] has recently indicated. It is to be recalled that he observed 11 patients with undescended testes among 260 boys between the ages of nine and 19 in a St. Paul day school, the average enrollment of which was 140 students. Inasmuch as the usual incidence of undescended testes is considered to be 1 in 500 (based essentially on military practice), it is immediately apparent that he was dealing with a most unusual incidence of the deformity. Even when it is admitted that its occurrence in children may be somewhat more

* It is to be noted (Table II) that in the bilateral cases reported in this paper upon whom semen examinations were made, only one (Case 1) was under the puberty age at the time of operation. A few of the bilateral patients operated upon at an earlier date were not available for purposes of the examination and others were too young to permit of the examination.

frequent than in adults engaged in military service, certainly the incidence of true failure of testicular descent is nothing like as common as Drake[6] found it in his series. Whereas the usual frequency with which undescended testes† are observed in the whole population is about 0.2 per cent, in males (adults and children) with hernia in whom retention of the testis is considerably more frequent than in the normal population, its incidence is still only one in 80 (Coley[3]‡) or 1.25 per cent. No mention of hernia is made in any of Drake's cases, yet the incidence of failure of descent is 4.2 per cent—a figure 21 times the normal frequency of the deformity. If the sample was consistent with the findings in a larger group, not more than one case should have been observed among 260 boys. This unusual incidence of so called testicular retention accompanied by subsequent spontaneous descent is explicable only on one basis, *viz.*, that a number of these were instances of so called "spastic retraction of the testis" for which physiologic ectopy or "ectopie en retour" are synonymous terms. Free mobility of the testis of the child appears to be the normal condition, and Hofstätter[10] reports instances of children who at will could draw their testes up into the inguinal canal. The writer has not infrequently been asked to operate for undescended testes in children where subsequent examinations have indicated that the testis is in the scrotum. Of three boys in one family with alleged failure of testicular descent, operation was necessary in only one to bring the testis down. The others were classed by me as instances of physiologic retraction of the testis.

The efficacy of the pituitary-like hormone, antuitrin S or follulutein, in effecting descent in bona fide cases of retention remains to be determined. To surgeons who have had the opportunity of noting at operation the mechanical restraint retarding descent, it is difficult to understand how the administration of a drug can overcome this hindrance. Whereas the normal process of descent of the testis may be accelerated in the macaque monkey as Engle[7] observed, it is not very likely that true failure of testicular descent will be repaired by its employment. Its use in the type of case reported by Drake would be accompanied by phenomenal success. It is not unlikely, however, that its employment may possess real virtue in infants with retained testes in whom fixation of the testis in its abnormal position is not as secure as in adults. In the larger number of patients operated upon by me for failure of testicular descent, the testis had come out of the external abdominal ring and had migrated up over the abdominal wall (so called superficial interstitial hernia). This portion of the journey, *viz.*, the distance between the top of the scrotum and the external abdominal ring is, as McGregor[15] has pointed out, the most hazardous for the testis. When the impulse for normal migration is still active in the testis, most is to be expected from a drug which enhances this migratory propensity. My associate, Dr. Charles Rea, has treated 14 patients between the ages of four and 24 with testicular retention with antuit-

† A patent funicular process is found in most patients with undescended testes whether actual hernia is present or not.

‡ In a recent discussion Coley[3] (Trans. Amer. Surg. Ass'n, vol. 51, p. 22, 1933) says that the incidence of undescended testes in 80,736 cases was 1,357 or 1.65 per cent.

rin S (Parke-Davis), giving usually one cc. (100 rat units) subcutaneously daily for a month. In the instance of a 24 year old boy the testis descended from the inguinal position into the upper portion of the scrotum, but it was later anchored by orchiopexy. Aberle and Jenkins[1] have previously reported somewhat similar experiences with the use of the pituitary-like hormone in effecting descent of the testis.

Unilateral Cases.—In unilateral cases of failure of testicular descent, the manner of dealing with the undescended testis probably would not be so

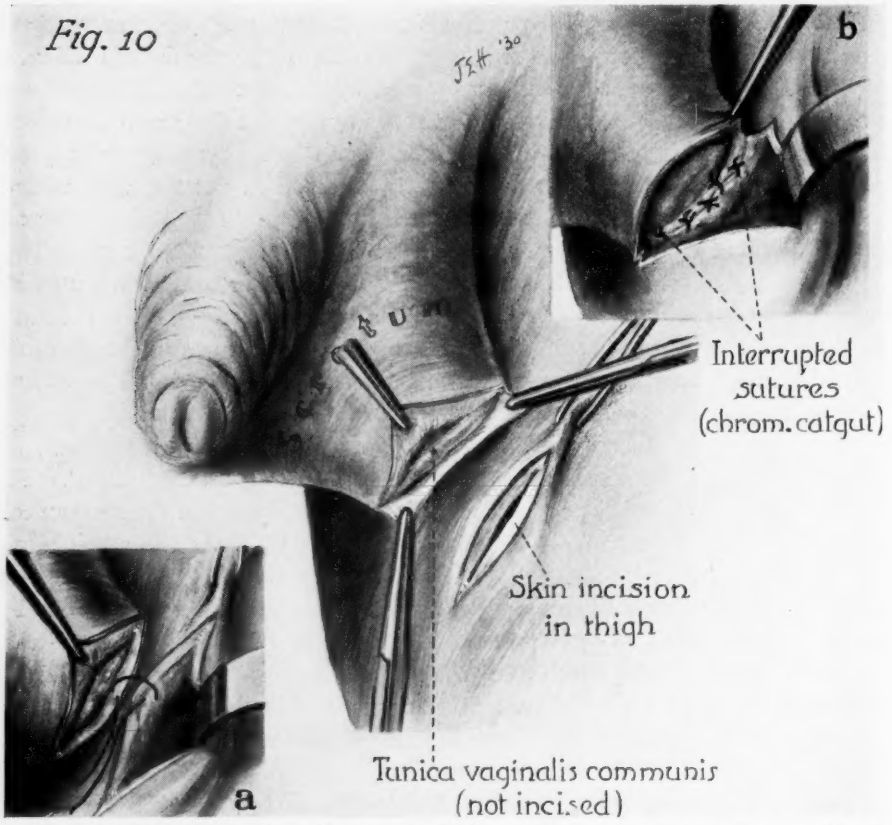

FIG. 10.—The Technic of Orchiopexy. Establishment of cutaneous juncture between skin of scrotum and thigh. (Courtesy S.G.O., p. 54, February, 1932, Fig. 10.) Since this illustration was made in 1930, the author has found that a cutaneous juncture one-third greater in length, as indicated in Figs. 11 and 12, insures a more satisfactory union. The posterior row of sutures is of chromic catgut 000.

readily agreed upon. My own feeling is that where the patient is still young enough to expect improvement in the status of the germinal epithelium by scrotal transference that orchiopexy should be done with the same indications in mind which prompts performance of the operation in bilateral cases. In patients past 30, the testis may be sacrificed without serious loss. The occasion which moves many surgeons to excise the unilaterally undescended testis "willy-nilly" is fear of malignancy. True enough, the retained testis, whether in the abdomen or in the groin, is more likely to become malignant than is the

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FIG. 11.—Four anchor sutures (ooo chromic catgut) are placed in the tunica albuginea of the testis and are brought down through the tunica vaginalis of the scrotum and anchored to the fascia of the thigh. The employment of the eye of a probe serves this purpose satisfactorily and obviates the occurrence of a large hole in the tunica vaginalis communis through which the testis may protrude, attending the employment of a hemostat to pull the sutures through. It is to be noted that the testis remains in the scrotum.

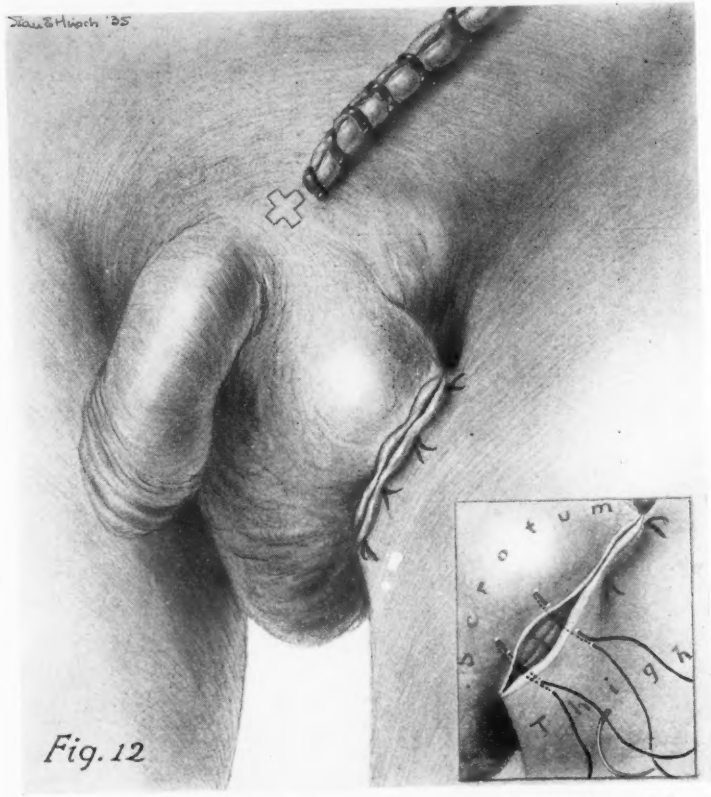

FIG. 12.—The orchiopexy completed. The sutures shown here are dermol and are usually left until the eighth to tenth day. Prompt healing of this cutaneous juncture is almost invariably obtained with careful placement of the sutures shown here. It has been the author's practice to leave this cutaneous juncture intact for about four months.

normal scrotal testis (probably about 50 times). Yet malignancy in the testis, whether scrotal or incompletely descended, is decidedly an uncommon occurrence. I am not persuaded that scrotal fixation of such a testis protects against the development of malignancy, for five cases have come to my notice in which malignancy occurred after orchiopexy. If one were to be consistent in his advocacy of the sacrifice of tissue exhibiting an increased disposition to the occurrence of malignancy, he should likewise advise the removal of the normal cervix and breast after their period of essential function is over—a position so absurd as not to warrant an attempt at vindication, even though malignancy of these organs is the most frequent cause of cancer deaths in the female. In this particular, it is necessary to differentiate between precancerous conditions and tissues which exhibit an increased likelihood to malignancy. The undescended testis belongs to the latter class.

In the performance of orchiopexy, a method must be used which will insure a low scrotal position for the testis. Counsellor[5] has recently discussed at some length the technical features to be considered. After noting the gradual ascent of the testis to a mid or upper scrotal position in many instances in which the Schüller-Bevan[19, 2] technic was employed, I have practised an operation of my own design which exhibits the advantage over the Torek* operation, that the testis remains in the scrotum and need not be transferred into the thigh. The technic of the procedure is nicely shown in the clear illustrations (Figs. 10, 11, and 12) made for me by Miss Jean Hirsch.

CONCLUSIONS

Observations on patients are reported in which spermatozoa were demonstrated in the semen after bilateral orchiopexy for failure of complete testicular descent. Proof of the presence of complete spermatogenesis in seminiferous tubules of such a testis is also presented. In pigs with retained testes which could be brought into the scrotum by orchiopexy, spermatogenesis was also demonstrated. It is apparent, however, in the human cases as well as in the pigs in which this deformity was corrected that satisfactory scrotal anchorage does not permit of the same uniform and diffuse restoration of mature germinal epithelium which attends scrotal transference of the normal (dog's) testis, temporarily elevated from the scrotum to the abdomen.

Whereas the results here reported would scarcely justify a stock-breeder in having bilateral orchiopexy performed on an animal with a valuable pedigree for breeding purposes, the virtue of orchiopexy in rectifying the sterility of cryptorchids (if still incompletely) warrants the performance of the operation in all suitable bilateral cases in man, for whom the right to procreate, and the blessings of paternity should be preserved inviolate. Apart from the con-

* The technic of orchiopexy known in this country as the Torek[22] procedure would more appropriately be termed the Keetley[12]-Torek operation. For though independently conceived and described, their striking similarity is apparent in a comparison of the illustrations of Mr. Keetley[12] and those of Doctor Meyer.[16] Dr. Franz Torek who probably better than any other individual has pointed out the necessity for adequate scrotal fixation in orchiopexy first described his operation in 1909[22] at which time he stated that credit for the new method belonged to Keetley.[12]

sideration of sterility, which does not concern unilateral failure of descent; the same indications which determine the necessity for operation in bilateral cases should be applied to unilateral testicular retention.

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DISCUSSION.—DR. LEONARD FREEMAN (Denver, Colo.).—I wish to take this opportunity to present a method of holding in place within the scrotum an undescended testis after it has been properly mobilized, which I have tried with satisfaction.

FIG. 13. FIG. 14.

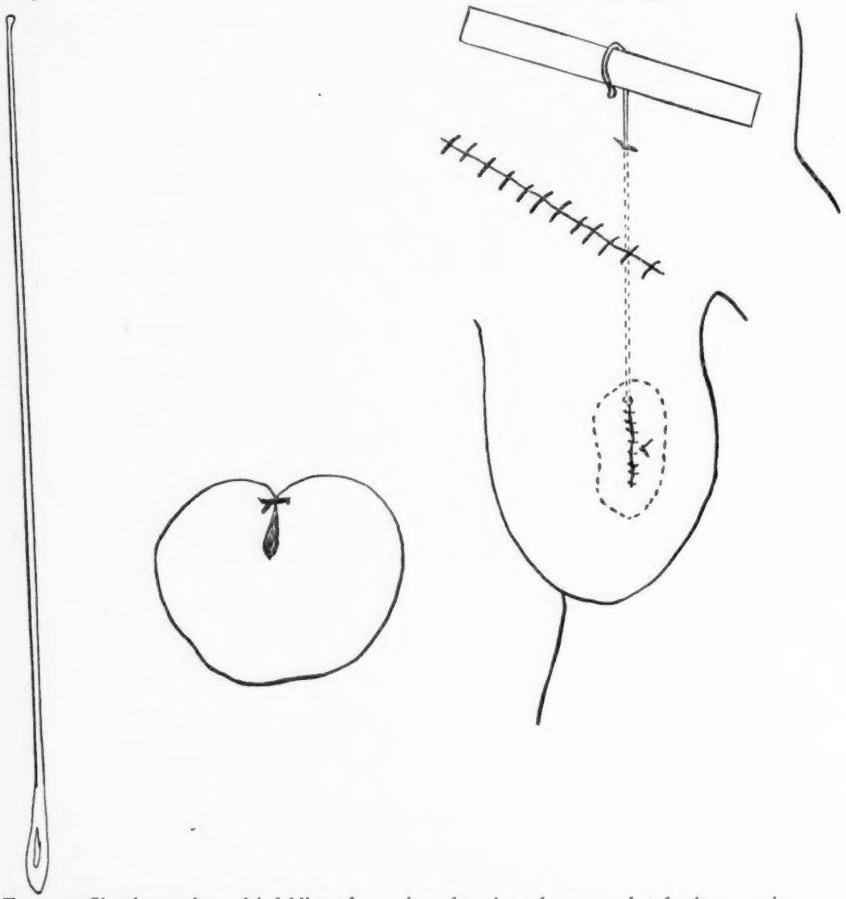

FIG. 13.—Showing probe and infolding of covering of testis to form a pocket for its reception.
FIG. 14.—Showing probe holding testis in position.

In this method the testis is held down by means of a long silver probe passed through a small hole in the skin of the abdomen a short distance above the inner end of the inguinal incision. The lower, or eye end of the probe, which may be looped on itself to increase its bearing-surface, is placed in a bed prepared for it by infolding the tunica vaginalis with chromic gut and for further security a suture of gut is passed through the eye or loop. The upper extremity of the probe is secured to the abdominal skin with a strip of sterile adhesive (Figs. 13 and 14).

The danger of infection is negligible, especially if the hole in the skin fits the probe snugly and an antiseptic dressing is used. (The fact that the probe is of silver also helps.)

At any time after the catgut anchoring suture absorbs, the probe can easily be pulled out from above. The patient can be out of bed promptly.

DR. FRANK TOREK (New York, N. Y.).—You have heard this very interesting paper of Doctor Wangensteen referring to the functional ability of the anchored testis. If we view what happens in the cases that were operated on by orchiopexy, it is very easy to see that the testicle increases in size. Also in many cases the patient himself develops remarkably after the testicle has been brought down, but the question of spermatogenesis is not nearly so simple.

The experiments by Moore, which Doctor Wangensteen has spoken of, are well known, but whether the same is true in the human species we cannot tell except perhaps by one clinical observation that I can cite. That is the case of a man whose testicles had been brought down by another surgeon but had slipped back again. He had been married a couple of years when I first saw him and brought down the testes. The marriage was childless. Eight years after the operation there was a child born to him. That child is now about ten or eleven years old and bears such a striking resemblance to the patient that the paternity can scarcely be doubted.

Of course, you can understand that it is very difficult to come to a conclusion concerning the establishment of spermatogenesis in the human species because we do not know whether those who are capable of procreating after the operation were possibly potentially capable before the operation. The difficulty is particularly great because these cases are usually operated upon in childhood so we cannot get any previous history as to spermatogenesis.

As to the matter of bringing down the testicle by means of a probe, I have no experience, nor have I any experience with the suction method, so I cannot discuss that.

As far as the attachment of the testicle is concerned, Doctor Wangensteen in a previous communication preferred to attach it by way of the dartos, attaching that to the thigh. I prefer to attach the testicle directly to the fascia of the thigh, even without the intervention of its tunica vaginalis. I have always turned that back so the testicle is directly attached to the high. The object of that is to give a good chance of getting additional nutrition from a new source.

In that respect it is very similar to the interesting paper we heard yesterday by Dr. Claude Beck, of providing new nutrition to the heart. He attaches the muscle directly to the heart, not to the pericardium, in order to give the heart a new source of nutrition.

Doctor Wangensteen mentioned Keetley. In my first paper on this matter I have given Keetley all the credit for being the first to bring down the testicle and anchor it to the thigh, although he did not attach it directly, but attached it by bringing down the gubernaculum and suturing that to the thigh. He said the gubernaculum is to be divided at a point as high up as possible, then turned down and attached to the thigh, in order, as he says, that the tension on the testicle may not be too great. You can see from that that his operation is a traction method, pulling down by main force, and with this precaution to reduce tension, he still finds it necessary to insist on strong flexion of the thigh in the after treatment.

Another surgeon who has brought down the testis by attaching it to the thigh is Katzenstein. In 1902 he operated, likewise with the employment of

forcible traction, for he says that, as soon as he let it go, it slipped back again. By main force he pulled it through a hole in the bottom of the scrotum and attached it to a flap of skin which he had dissected from the thigh. The operation was successful as far as bringing down the testicle, but it made an ugly appearance after the flap had been cut off from the thigh and sutured to the scrotum.

Another surgeon who performed orchiopexy is De Beule, a Belgian. He reported two cases in which he had attached the testicle directly to the fascia of the thigh. This attachment, however, was also done by the traction method. He describes how very tensely stretched the cord was.

There are points in De Beule's article of November, 1906, which for various reasons fail to be convincing. Thus, he claims priority over Keetley because the first of his own two cases was operated on in 1904, whereas Keetley's paper appeared in 1905. But if De Beule read Keetley's article, he ought to have known that at that time Keetley had already operated upon more than 25 cases. Moreover, Keetley had already shown cases in 1894 and had published them in the Lancet in April, 1894. (I may also say, in passing, that I had already shown some of my cases at the New York Academy of Medicine before De Beule's article appeared. Furthermore, in De Beule's article there is an illustration of his second case, three and one-half years old, a unilateral orchiopexy, recently performed, for the gauze dressing of the posterior suture is still in place, showing the scrotum of the attached testicle to be very well developed, not stretched but hanging, although the picture was taken shortly after the operation, and the other testicle and scrotum on the unoperated side exceptionally large. It almost looks as though this might have been a testicle that would have come down by itself. But at any rate, the priority of anchoring the testicle to the thigh decidedly belongs to Keetley and not to De Beule or Katzenstein.

Dr. Frank K. Boland (Atlanta, Ga.).—I would like to call attention to a non-operative method of treating the undescended testis as practiced by my urologic friends, Doctors Ballenger, Elder and McDonald, in Atlanta. The method was instituted by them 15 years ago to develop the size of the penis. That the treatment would also prove effective for undescended testis did not at first occur to them, but it soon became evident that while the suction which was employed enlarged and pulled down the penis and scrotum, it had the same effect on an undescended testis. The treatment is used when hormones have failed, or as an adjuvant to hormones. The apparatus consists of a glass cylinder somewhat larger than the barrel of a 100 cc. syringe. A rubber ring surrounds the open end of the cylinder, while to the small nozzle at the other end is attached a rubber tube which is connected with a water pump. The patient's pubes is well soaped, and the penis and scrotum enclosed in the cylinder which is pressed airtight against the pubes. The water pump is supplied with an indicator which shows the amount of vacuum that is generated in the cylinder, the average suction used being equivalent to from five to 30 pounds. The best indicator, however, is the amount of vacuum which the patient can endure comfortably. Treatments usually are given two or three times a week, for from two to ten minutes on each occasion. Suction causes the parts to enlarge and elongate three or four times their usual size, the vacuum being maintained from five to 20 seconds with each suction. The vacuum is immediately discontinued by a turn valve at the distal end of the cylinder, or by a foot control. As soon as the patient feels that he has all the pulling he can stand, the vacuum is cut off, another suction being instituted a few moments later.

Twenty-six patients have been treated in this manner, of ages from four to 16. One of the best results occurred in the 16 year old boy, who is now a doctor, married and raising a family. However, the most successful cases have been in boys from six to eight years old. The majority of these patients have had perfect results, the penis, scrotum and testes being full size, and the testes being drawn well down in the scrotum. I have seen two such satisfactory results. The length of treatment has varied from one to six months. The patients not completely cured either were too old or did not continue the treatment long enough. It is believed that this vacuum method is capable of correcting undescended testis in any boy of the right age. It is no doubt true that the testis may have descended in some of these patients without treatment. One of the authors of the method thinks testes in the abdominal cavity should first be transplanted into the inguinal canal by operation, and then subjected to vacuum therapy; while another author is of the opinion that the testis can be drawn down by suction, no matter how high it may be. A striking outcome of the procedure is that not only are the external genitalia made normal, but the feminine characteristics, which so many of such patients display, are made to disappear. They lose weight, and the hips and breasts become masculine in contour. No serious trauma by the treatment has been noted. One patient developed a slight ecchymosis at the base of the penis, which lasted only a few days. I inquired if such manipulation of the genitalia ever led to masturbation, but was informed that no such sequel has been reported.

Dr. Arthur D. Bevan (Chicago, Ill.).—I believe the successful handling of undescended testis is a matter of anatomy, a very careful study at that. In undescended testis, in the operation, one must free the testicle perfectly by the removal of the transversalis fascia, the vaginal process of peritoneum, the cremasteric muscle, and fascia, and intercolumnar fascia, so that you really free the testicle completely from the coverings of the cord.

In that way you can obtain lengthening of the cord, depending upon the age of the child or individual from two to five inches (Fig. 15). Where you can obtain sufficient lengthening so that the testis can be placed in a pocket made in the scrotum without any tension, you can secure admirable results without any fixation to the thigh or any other artificial means (Fig. 16). In order to retain the testis in the scrotum, a fine suture should be placed at the neck of the scrotum in front of the cord; care should be taken in placing this suture so that it can in no way interfere with the blood supply of the testis.

There is one point that we have employed in the technic which is interesting and important. For about five years, we have been passing a needle through the strong fibrous coat of the testis, and double threading a piece of catgut or, you can take silk, if you please, and after you have made a large pocket in the scrotum, pass a straight needle on a director through the bottom of the scrotum (Fig. 17), carrying this catgut with it so you have a guide, held by an assistant, holding the testicle well down in the pocket while you close the neck of the scrotum (Fig. 18). After the operation is completed this temporary guy rope is removed.

In regard to antuitrin, it seems to me we have to keep our feet on the ground in a problem of this kind—it is a common sense problem. What in the world do you want to use it for even though you can produce an early development of the testis in a young child? Why should you give a child of five or six or eight years of age a hormone that would develop the testicle? As a matter of fact, I think in no cases of pure, undescended testis, even though

you can increase the size of the testis very considerably, would you bring the testicle down except in a special class of cases which I have described, which indeed forms a very considerable class. At least in a quarter of the cases that are sent to us to operate upon are not undescended testis cases at all. If you run your fingers down the groin in these cases, you can push the little testicle

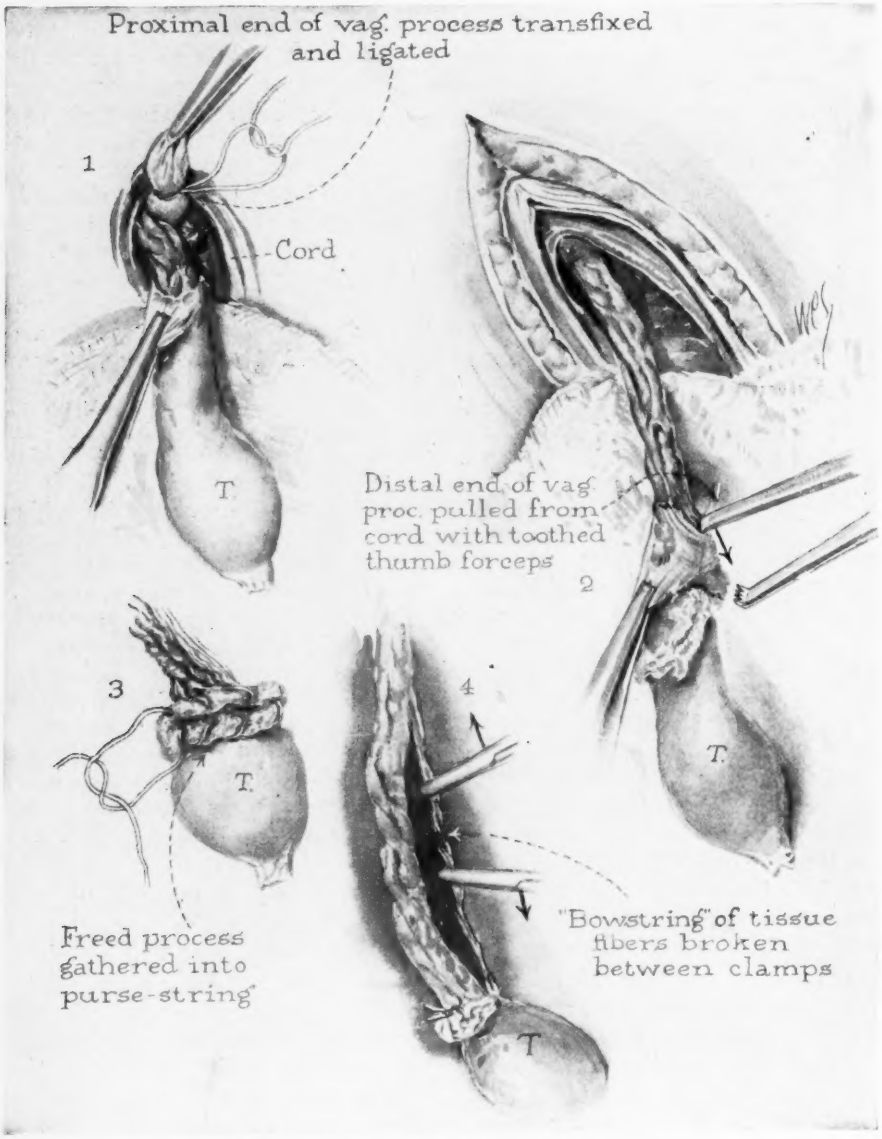

FIG. 15.—Technic of orchiopexy (Bevan).

right into the scrotal pocket. When you take your fingers off, they return; but at puberty with the enlargement of the testis they drop down into the scrotum of their own accord. We have had a large experience with this type of case, at the age of puberty, with the enlargement of the testis, they drop down into the scrotum and develop normally.

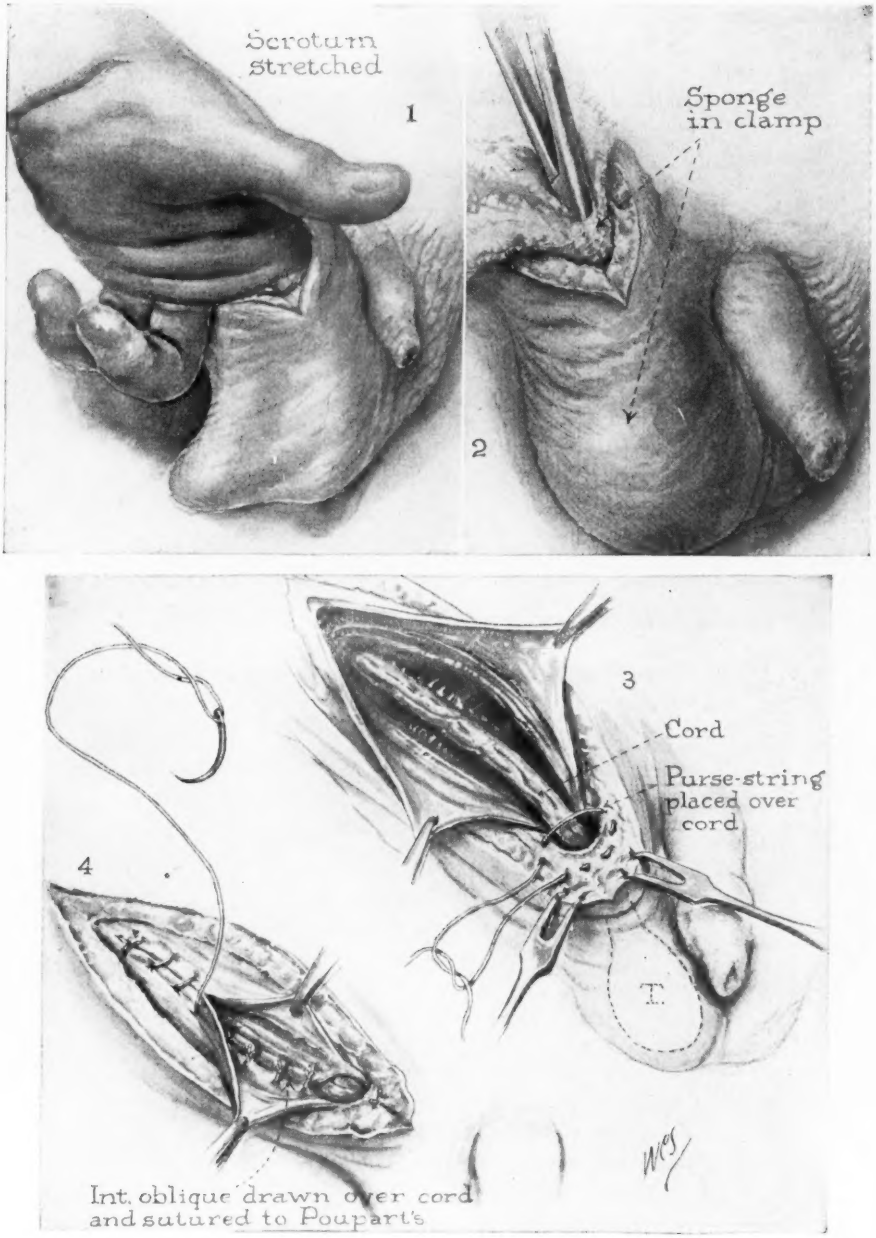

FIG. 16.—Technic of orchiopexy (Bevan).

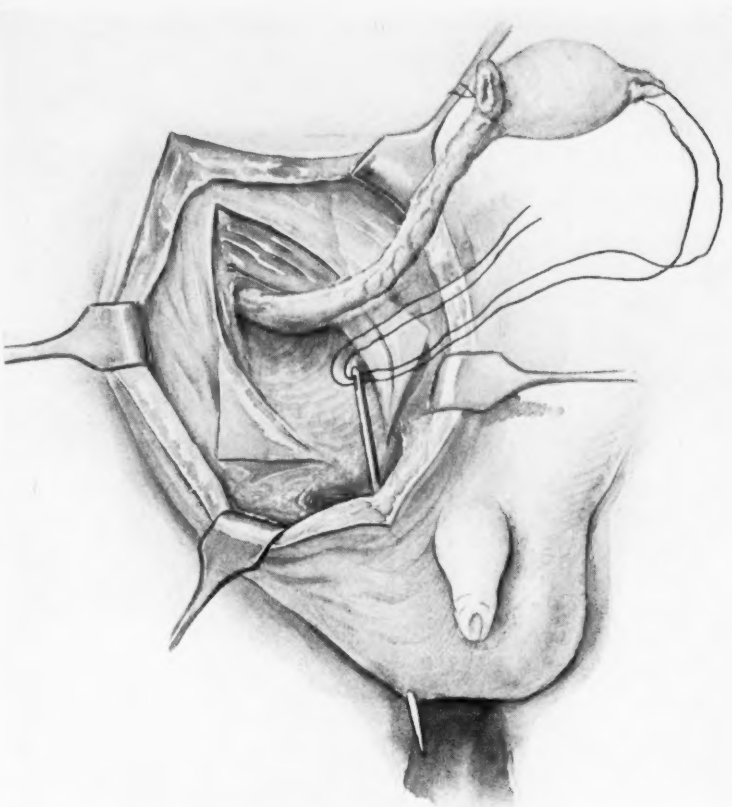

FIG. 17.—Technic of orchiopexy (Bevan).

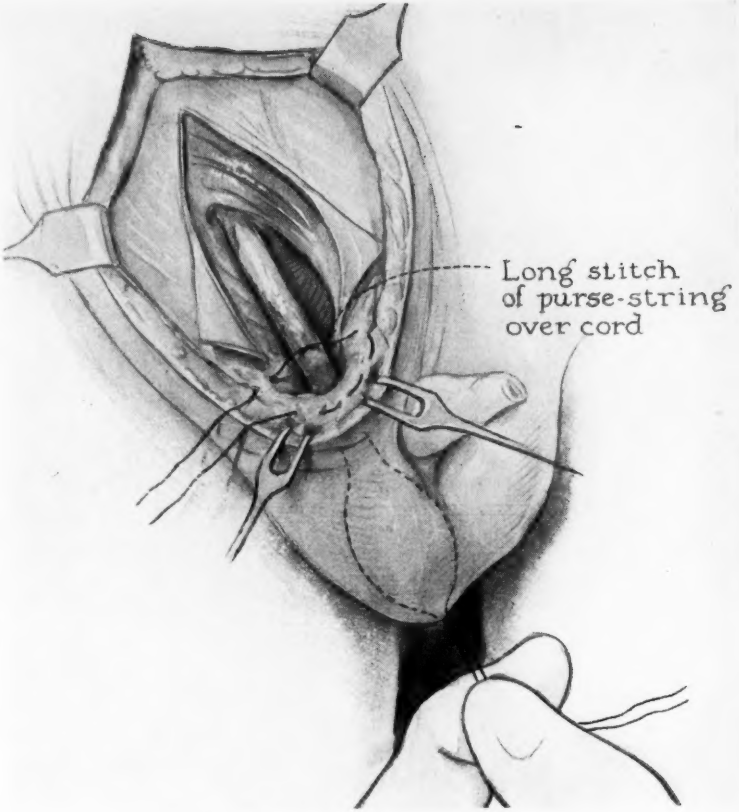

FIG. 18.—Technic of orchiopexy (Bevan).

DR. WILIAM B. COLEY (New York, N. Y.).—The subject of undescended testis is one that has interested me since 1893 when I did my first operation. I am quite in accord with what Doctor Bevan has already said. I do think it is an anatomic problem and while I am willing to admit the results of bringing the testis and fixing it in the thigh are somewhat nearer ideal than the results following the operation Doctor Bevan described in the late nineties and 1901 and 1903, I do not believe that the results of this method are so much inferior to that of Torek as to warrant adopting the latter as a routine measure.

I believe the great majority of cases of undescended testis, if operated upon at the proper time, can be put in the bottom of the scrotum, and a very large number will stay there; some will retract to the middle of the scrotum, and some to the external ring. I do not believe that spermatogenesis has anything to do with the malposition of the testis. This is an opinion that I expressed in 1914 at the meeting of the American Surgical Association before which I reported 414 cases of operation for undescended testis, of which 40 were in adults.

Unfortunately, few surgeons attempt to follow up cases that have been operated upon for undescended testis. In a series operated upon by Doctor William A. Downes and myself at the Memorial Hospital, we traced 125 cases from two to 20 years, which is the longest period ever traced. While the results, in our opinion, were not perfect, they were very fairly satisfactory: there were no deaths in the entire series, and no return of the potential hernia that always exists.

As to the frequency, I was quoted correctly; *i.e.,* one sixty-fifth of one per cent. I made a study many years ago of 80,000 cases of inguinal hernia in the male, observed at the Hospital for Ruptured and Crippled, as regards relative frequency of undescended testis, and in this number I found 1,757 undescended testes.

Taking operative statistics, in 1908 in 4,000 cases of inguinal hernia in the male, we operated upon practically 7½ per cent of undescended testis; in adults, the percentage was only 4.7. But I do not believe the question of the functional value of the testicle depends at all upon the place where the testicle is found or put. I do not think you can tell anything about it by animal experimentation either. The only way of telling whether the undescended testis is of functional value is to study the history of the cases you have operated upon for double undescended testes.

I have had two cases of double undescended testes in both of which the patients become fathers of children. In both, the testes were brought down into the scrotum in the way outlined by Doctor Bevan, and not attached to the thigh. My feeling today is, that while the Torek operation is an admirable one and usually gives ideal results, it is unnecessary to perform such an extensive operation in the great majority of cases, especially in children.

Regarding the age at which to operate: we formerly operated upon children as young as four or six years old; but we later came to believe that it was unwise to operate under 12 years of age because we learned by observation that in a large number of cases the testis will come down voluntarily if given time, thus avoiding an operation.

DR. OWEN H. WANGENSTEEN.—This is obviously a very broad subject and time will afford me opportunity to comment only briefly on a few points in the discussion. The novel suggestion of Doctor Boland is very intriguing. I am inclined to believe, as Doctor Bevan so well put it, that a rather large number of patients with alleged failure of testicular descent, cured of their deformity by non-operative methods, are afflicted with a condition known as

spastic retraction of the testis rather than true failure of descent. Any one who has done a number of operations for the correction of incomplete testicular descent cannot escape the impression that the mechanical element is an important one in hindering the spontaneous descent of the testis into the scrotum when once it has become arrested in the groin. At operation, almost invariably, it is found necessary to remove many little fibrous kinks and bands from about the spermatic cord before the testis can be brought into the scrotum. I have seen no instance at operation in which a pull upon the testis and spermatic cord by the surgeon would permit the testis to be placed in the scrotum. A sage renowned for his wisdom once said: "To every thing there is a season, and a time to every purpose under heaven." Though I admit considerable trust in the principle of suction, as some of you may know, I cannot believe that this is a place for its employment.

With reference to the remarks of Doctor Torek, I should only like to remind you that as far as is known, the blood supply to the testis in instances of incomplete descent is quite adequate. I venture to suggest that were the blood supply of the testis deficient that mere placement of the testis in the thigh would not permit it to eke out of this new potential source sufficient nutriment to enable the testis to repair the deficiency in its germinal epithelium.

It is my belief, supported by experience, that some means of adequately fixing the testis in the lower part of the scrotum is a highly essential feature of the operative procedure of orchiopexy. If uniformly good results are to be had, adequate fixation of the testis must be afforded. The facility with which the testis may retract after orchiopexy, when not fixed, is certainly a matter of common knowledge and experience. The elements to which responsibility may be attributed for the retraction are the components of the spermatic cord and the dartos muscle of the scrotum. The cremaster muscle is invariably cut away in the operative procedure, hence it can play no rôle. The vas deferens is relatively inelastic. The blood vessels, on the contrary, are quite elastic and are no longer than they have to be. I believe that the blood vessels together with the dartos muscle may be held accountable for retraction of the testis after orchiopexy when testicular fixation is not employed. As to the means of fixation employed, it must be a method which will hold the testis down for some time. In my own experience, a suture fastened to the testis and anchored to the thigh is inadequate; within a few months the testis retracts to the upper portion of the scrotum.

A well tempered doubt, as manifested by Doctor Coley is of the greatest virtue in any experimental problem. When, however, he affects to deny any relationship between spermatogenesis and an aberrant position of the testis, he denies the facts. That the normal testis becomes aspermatic when elevated out of the scrotum has long been known; that its return to the scrotum restores spermatogenesis has likewise been established. The results of this study indicate that improvement in the germinal epithelium attends satisfactory scrotal anchorage of the undescended testis in man as well as in the pig. It is to be freely admitted, moreover, that restoration of a mature spermatogenesis does not occur in the same measure, after orchiopexy for undescended testis, as attends return to the scrotum, of a normal testis, previously elevated to the abdomen. The reason for this difference remains yet unexplained, and may well lie, as Doctor Coley implies, in an inherent diminished capacity of the undescended testis.

SUBACUTE STREPTOCOCCUS VIRIDANS SEPTICEMIA

CURED BY THE EXCISION OF AN ARTERIOVENOUS ANEURYSM OF THE EXTERNAL ILIAC ARTERY AND VEIN

WILLIAM F. RIENHOFF, JR., M.D., AND LOUIS HAMMAN, M.D.

BALTIMORE, MD.

FROM THE MEDICAL AND SURGICAL CLINICS OF THE JOHNS HOPKINS HOSPITAL, BALTIMORE, MD.

ON JANUARY 21, 1935, a young man was referred to us for examination who had been ill with fever for six months. A brief story of the illness and a summary of the results of the examinations which were made follow:

CASE REPORT

Unit History No. 60223, Mr. J. A. W., an oil salesman, 35 years of age, entered the Johns Hopkins Hospital, January 21, 1935, complaining of weakness, loss of weight and fever of six months' duration. Before the onset of this illness he had always been a healthy man. He had had several of the minor infectious diseases of childhood. At 26 the tonsils had been removed. The only point of interest relative to the recent illness was that at 18 years of age, May 18, 1918, the patient had accidentally shot himself with a 22 caliber rifle, the bullet penetrating the abdomen just above Poupart's ligament. Immediately after the accident, the patient was able to walk about 50 yards. He had a very severe burning sensation in the right leg and bled profusely from the bullet wound. His companions placed a tourniquet around the thigh which stopped the profuse bleeding, but the patient had lost so much blood that he fainted repeatedly while being transported eight miles to the nearest hospital. That evening he was operated upon by Dr. A. M. Willis at the Virginian Hospital in Richmond. After the operation he was informed that the bullet had torn a hole in the two large vessels which supply the right leg, and had established an arteriovenous communication between them. An extensive retroperitoneal hemorrhage had occurred. The injury was followed by pronounced swelling of the right leg and for a while the patient was completely disabled. After a few weeks, however, the swelling disappeared and gradually he was able to use the leg more and more until finally at the end of two months he could walk about without the use of a cane. During the next six months there was occasionally some swelling of the ankle in the late afternoon and evening. If the patient exerted himself unusually, cramp-like pains in the leg would come on which, as time progressed, became less pronounced. All symptoms of the injury had disappeared at the end of a year excepting some nocturnal palpitation of the heart, and the consciousness of a vigorous pulsation in the right lower quadrant of the abdomen. There had never been any dilatation of the veins of the right thigh, leg or foot; no changes in the skin; none in the bones by roentgenologic examination; and the length of the right and left extremities was the same. In 1932 the patient was examined by Doctor Caravati who found no abnormality except the presence of an arteriovenous aneurysm in the lower right quadrant of the abdomen together with moderate enlargement of the heart associated with a rapid pulse, varying from 100 to 120 beats per minute.

The patient's recent illness dated from July, 1934, when he began to feel listless and generally indisposed. His temperature was taken and it was found that each afternoon it rose to about 100°. A little later his appetite failed and in a short time he lost 30 pounds in weight. The patient's symptoms were thought to be the result of a mild throat infection. However, although the local manifestations promptly cleared up under treatment, the fever and lassitude persisted. In September he had a number of severe chills and the possibility of malaria was considered and he was given large doses of quinine.

Under this treatment the temperature dropped to a lower level but the patient's general condition did not improve. At the end of September he was so weak and miserable that he went to bed and remained there up to the time of his admission to the hospital.

During the intervening four months the condition had been very thoroughly investigated but no satisfactory diagnosis had been reached. The possibility of amebic dysentery was considered and he was treated with emetine, but without benefit. The fever persisted and he continued to lose weight and strength. Doctor Caravati took charge of the patient in October, 1934. At that time the physical examination showed emaciation, pallor, enlargement of the liver and spleen and the presence of the arteriovenous aneurysm. Agglutination tests with strains of Brucella were negative. With the typhoid bacillus, agglutination occurred in a dilution of 1:200. The patient had received prophylactic typhoid vaccine about seven years before. On a number of occasions occult blood was found in the stools. The blood showed a mild secondary type of anemia. During October there was a slight leukocytosis but this soon disappeared and later the leukocyte counts varied from 6,500 to 9,000. Roentgenographic examination of the gastro-intestinal tract revealed no abnormality. Fourteen blood cultures had been made and all were reported negative.

Physical Examination.—Temperature, 101°; pulse, 110; respirations, 22; blood pressure, systolic 110, diastolic 60.

The patient was an undernourished man with a sallow, anemic complexion. He had evidently lost much weight and his appearance showed evidences of prolonged illness. Aside from his weakness and lassitude, he otherwise felt well. He had no pain or other local discomfort. No petechial spots were noted in the mucous membranes or in the skin. The eyes were normally prominent. The pupils were equal; they reacted actively to light and accommodation. Inspection of the fundi revealed no abnormality. The teeth were in good condition. The pharynx showed nothing remarkable. The tonsils had been completely removed. There was no enlargement of any of the superficial lymph nodes. The thyroid was not enlarged. The chest was rather long and thin with a narrow costal angle. It was symmetrical and the movements were equal on the two sides. The percussion note over the lungs everywhere was resonant and the breath sounds were vesicular. No râles were heard. The area of cardiac dulness was not enlarged. The heart sounds were clear and of normal quality except for a loud, systolic murmur in the pulmonary area. The pulse was regular, of high amplitude and a little quick though by no means collapsing in quality. The abdomen was normal in appearance. The walls were soft and relaxed. The edge of the liver could be felt about a finger's breadth below the costal margin; the border was rounded and the organ of normal consistency. The edge of the spleen was easily felt about a finger's breadth below the costal margin and was a little tender. In the right lower quadrant there was an intense, continuous thrill on light palpation which was associated with marked excursion of the iliac vessels. On deep palpation the difference between the size of the iliac vessels on the right compared with the normal vessels on the left was very striking. The vessels on the right side were many times larger than on the left. By exercising firm pressure it was possible to obliterate the fistulous opening, thereby causing a cessation of the continuous thrill. It was interesting to note that occlusion of the opening did not bring about perceptible slowing of the pulse rate,* indicating that the fistulous communication was probably a small one. A hard, bony-like structure could be felt about the mass which the roentgenogram proved to be the calcified wall of the encysted varicose aneurysm. There was vigorous pulsation in

* Previously called Branham's sign, but this phenomenon was first described by Nicholadoni, Phlebarteriektasie der oberen Extremitat. Arch. f. klin. chir., vol. 18, p. 252, 1875. Branham in 1890 made an independent observation of this reaction in traumatic arteriovenous aneurysm. Cf. Dr. Dean Lewis (1) Congenital Arteriovenous Fistulae. Lancet, September 20, 27, 1930; and (2) The Bradycardiac Reaction and the Cardiac Changes in Arteriovenous Aneurisms. Emanuel Libman Anniversary Volumes, 1932. International Press, New York.

the external iliac artery just above Poupart's ligament and in the femoral artery below. A strong pulsation was easily felt in the dorsalis pedis and posterior tibial arteries. Auscultation over the aneurysm revealed the classic machinery-like to and fro bruit which was markedly diminished in intensity by deep pressure on the upper portion of the external iliac artery. There was no evidence of the development of a collateral circulation about the hip or thigh. There were no varicosities of the veins distal to the point of the fistulous communication. There was no swelling or edema of the soft parts of the thigh, leg or foot. Blood pressure readings:

	Systolic	Diastolic
Right arm	120	55
Left arm	125	45
Right thigh	60(?)	40(?)
Left thigh	120	55

The skin temperature of the right and left lower extremities was essentially the same. When deep pressure was made over the external iliac artery above the fistulous communication there was marked diminution in the blood flow through the femoral artery, but no difference occurred in the appearance of the skin of the right extremity or in its temperature. These observations confirmed the impression that the fistulous communication between the external iliac artery and vein must be a small one. Since there was no change in the temperature or appearance of the skin following deep pressure over the upper part of the external iliac artery, we concluded that the collateral circulation which had developed would be sufficient to prevent serious embarrassment of the blood supply to the extremity should the external iliac artery above the fistula be permanently occluded. The extremities otherwise showed no abnormality, no arthritic manifestations, no clubbing of the fingers. The deep reflexes were normally active.

Laboratory Examinations.—Blood count: hemoglobin, 68 per cent; red blood cells, 3,650,000, white blood cells, 10,000. Differential: Polymorphonuclear neutrophiles, 65 per cent; lymphocytes, 32 per cent; monocytes, 3 per cent. Wassermann reaction on the blood serum negative. Van den Bergh test negative.

Agglutination tests: *Bacillus typhosus* positive up to dilution of 1:320. Paratyphoid B positive up to dilution of 1:320. Paratyphoid A., Shiga's bacillus, Flexner's bacillus, Brucella's abortus—all negative.

Blood cultures: 1/23/35, *Streptococcus viridans*, 28 colonies per 1 cc. of blood. 1/29/35, *Streptococcus viridans*, 20 colonies per 1 cc. of blood. 2/6/35, *Streptococcus viridans*, 49 colonies per 1 cc. of blood.

Urine: Specific gravity ranged from 1.010 to 1.020. Contained neither albumin nor sugar. A few pus cells in the sediment. No red blood corpuscles or casts. Urine culture: No growth. Stool: No gross blood or mucus. Benzidine test negative. Microscopically some undigested vegetable material, otherwise negative. Intracutaneous tuberculin test: No reaction.

Roentgenologic Examination.—Abdomen.—An elliptical body clearly defined by calcified walls overlying sacro-iliac joints. The appearance of this structure is compatible with the diagnosis of arteriovenous aneurysm. A bullet is located oposite the third lumbar vertebra on the right side. Chest.—Increase of the shadows about the middle border of the lungs due probably to chronic passive congestion. There are no areas of bronchopneumonia. The heart seems not to be enlarged. Tele.—M. R. 5.5, M. L. 9, A. 5.5, T. 28.5.

Electrocardiogram.—Rate 115. Rhythm sino-auricular. P-R interval .14, QRS duration .08. Normal sinus rhythm. T I and II upright. T III inverted. Ventricular complexes are sharply defined. Sinus tachycardia.

Discussion.—These observations demonstrated conclusively that the patient was ill with *Streptococcus viridans* septicemia but it was not clear

precisely where the infection was located. It is well known that the *Streptococcus viridans* often invades the blood stream, sometimes even in large numbers, when there is an acute septic infection, for instance, a severe acute sinusitis. However, under these circumstances the septicemia is brief, for the organisms at once disappear from the blood when the acute infection subsides. Certainly there was nothing in the situation which then held our attention to encourage the sanguine hope that the septicemia might be such an acute and transient one. Quite otherwise, for all the facts (the long duration of the illness, the persisting fever, the anemia, the enlargement of the spleen, the repeatedly positive blood cultures) demonstrated that there must be a focus of infection having direct access to the blood stream and continuously discharging bacteria into it. When we observe a clinical picture so characteristic as this one was we conclude that the focus of infection is in the heart, because wide experience has taught us that under these circumstances it is nearly always situated in that organ and, save for rare exceptions, upon the valves. Therefore we confidently expect to discover the unmistakable evidence of a valvular lesion and if the infection has existed for some time our expectation is seldom disappointed.

The remarkable thing about the present case was that the anticipated evidence of a valvular defect was completely wanting. It may be that the heart was a little enlarged (the measurements of the teleroentgenogram being a trifle more than half the transverse diameter of the chest) but some enlargement might be expected to follow as a result of the circulatory alterations caused by the arteriovenous aneurysm. The heart sounds were clear and of normal quality except that there was a systolic murmur at the pulmonary area. In the presence of anemia and long-continued fever it would be noteworthy if a systolic murmur did not appear at the pulmonary area.

Being convinced by repeated examinations that the infection was not located upon the heart valves, two possibilities suggested themselves (a) that the vegetations were upon the endocardial surface of the chambers of the heart or (b) that they were situated within the arteriovenous aneurysm.

The occurrence of vegetations upon the endocardial surface of the auricles or ventricles is one of the common observations of the pathologist. Almost every case of subacute bacterial endocarditis will show them, where they have extended directly from the diseased valves or where they have become implanted from the infected valve which, floating to and fro, has rubbed against the endocardial surface. These are familiar observations, but it is another matter to ask whether bacterial vegetations upon the inner surface of the chambers of the heart ever occur as primary foci of infection, that is, when there is no valvular disease or congenital defect. No note of such an occurrence can be found upon the pathologic records of the Johns Hopkins Hospital and both Dr. W. G. MacCallum and his associate, Dr. A. R. Rich, tell us that they have never seen an instance of it. Therefore, if it ever happens it must be a great rarity. The fact that no evidence was noticed of embolic phe-

nomena in the general circulation was a point against the infection being located within the left side of the heart.

Unfortunately the localization of bacterial vegetations within an arteriovenous aneurysm must occur almost as uncommonly as their isolated growth upon the endocardial surface of the heart. A review of the literature failed to disclose a reported example of the condition. Nevertheless there are many observations which led us to believe from analogy that bacteria might settle and grow within an arteriovenous aneurysm. We refer to the observation of *Streptococcus viridans* vegetations about the orifice of a patent ductus botalli or at the site of coarctation of the aorta. We recall also an instance in which bacterial vegetations were situated within an aortic aneurysm. These are clear demonstrations that bacteria often lodge and grow upon the intima of the aorta at points where the vessel is constricted or its walls damaged by disease. From mechanical standpoints an arteriovenous aneurysm is very similar to an open ductus botalli.

These considerations led us to believe that in the present case, in all probability, the *Streptococcus viridans* had settled and grown within the arteriovenous aneurysm and from this site of advantage continuously poured bacteria directly into the blood stream. Should this be the case then, we reasoned, the septicemia might be cured and the patient restored to health by excision of the aneurysm. The possibility of gangrene of the leg setting in after ligation of the right external iliac artery was discussed, but upon this point the surgical opinion was entirely reassuring. The *Streptococcus viridans* is an organism of mild virulence. The view generally held is that it would disappear at once from the blood stream were there not present a focus from which fresh bacteria are constantly discharged into the circulation. As we have already said, the sudden flooding of the blood stream with *Streptococcus viridans* in connection with an acute infection which soon subsides is relatively an innocuous affair.

As matters then stood the outlook for the patient under conservative treatment was almost hopeless. Study of anatomic specimens teaches that many patients get well of bacterial endocarditis. This anatomic evidence, however, is so glaringly in contrast to clinical experience that we are forced to conclude that most of those who recover must have had such mild symptoms that the infection passed unrecognized. When the typical clinical manifestations of subacute *Streptococcus viridans* septicemia are once fully developed recovery does not often follow. Therefore it was more than likely that the patient would die were no radical measures undertaken.

On the other hand, excision of the arteriovenous aneurysm, should the infection be located there, held out the bright prospect of cure. It seemed to us that to perform the operation was risking little in the hope of very great gain. The situation was plainly and fully explained to the patient and his wife. Both enthusiastically chose operation.

Operation.—As the illustration (Fig. 1) shows, the enormously dilated right common and external iliac arteries, overlain by the right ureter, presented in the operation wound.

To the left and coursing along the medial side of the external iliac artery, the very much dilated and thin-walled external iliac vein joined with the internal iliac to form on the

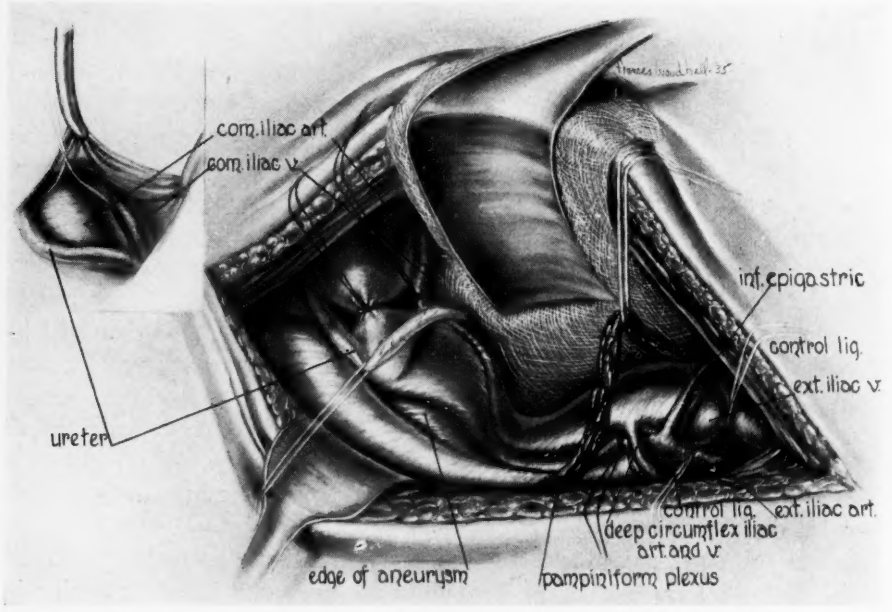

FIG. 1.—Drawing, made at operation, of the dissection of the arteriovenous aneurysm between the external iliac artery and vein. Control ligature about external iliac vein was used as permanent ligature, but the control ligature about the femoral artery was removed, a permanent ligature being placed proximal to the departure of the deep circumflex iliac artery.

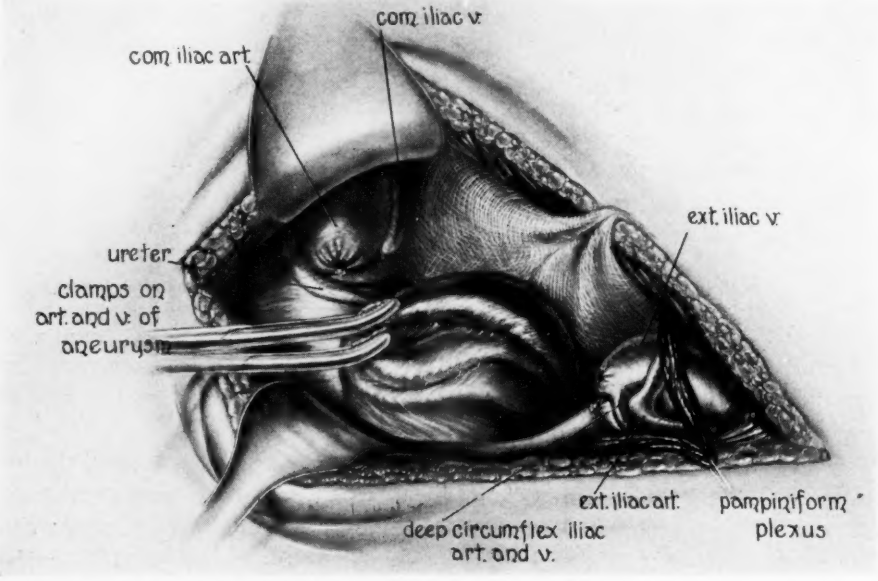

FIG. 2.—Four cardinal points have been ligated and aneurysm has been removed.

posterior surface, deep beneath the artery, the common iliac vein. All the visible tributaries of the external iliac vein, *i.e.*, the femoral, deep circumflex iliac and deep epigastric

veins were very much dilated. The admixture of arterial and venous blood could readily be seen through the thin walls of the venous channels. The medial edge of the common iliac vein could just be observed along the corresponding margin of the right common iliac artery. Normally the vein at this level is covered completely by the artery. The main, dilated portion of the vein was also concealed by the common iliac artery, creating the false impression that the diameter of the common iliac vein was much smaller than that of the external. However, on further dissection this was found not to be the case. Distal to the fistulous opening the external iliac artery was of normal size, or perhaps even smaller. On the posterior lateral surface of the artery, lying on the iliacus muscle, was an oval, hard mass, like a hollow chamber, which was connected with the artery and also the vein. One could feel a continuous thrill through its wall. The surrounding adhesions to the artery and the posterior position of the vein and fistula together with the calcification of the aneurysmal sac made separation of the individual vessels and an attempt to close the fistulous opening impractical and because of the size of the vessels, very dangerous. The common iliac artery and vein therefore were separated by blunt dissection and a control ligature placed about the former. The same procedure was carried out on the external iliac artery and vein. The ureter and overlying pampiniform plexus were removed from the surface of the vessels, which were then exposed throughout their continuity. Permanent ligatures of oiled braided silk were placed at the four cardinal points; *i.e.*, below the fistula, around the external iliac vein distal to the entrance of the deep epigastric and circumflex iliac veins; about the external iliac artery proximal to the departure of the deep circumflex iliac and epigastric arteries; above the fistula about the dilated common iliac vein and artery; and about the internal iliac vein (Fig. 1). The control ligatures were removed and after pulling the permanent ligatures home the aneurysm was excised (Fig. 2). Some difficulty was experienced in controlling the bleeding from dilated collateral vessels on the posterior surface of the aneurysmal sac as these vessels were very short, thin-walled and were held patent by the iliacus fascia.

The size of the vessels in the immediate vicinity of the aneurysm would seem to be worthy of record. The right common iliac artery proximal to the fistula was about the size of a normal aorta (Fig. 2). The left common iliac artery was perfectly normal in diameter. The portion of the external iliac artery proximal to the fistula was dilated to the same size as the common iliac and there was some increase, but by no means so great, in the diameter of the internal iliac. The external iliac artery distal to the fistula was of normal size. The deep epigastric and circumflex iliac arteries appeared to be larger than normal. When the permanent ligature about the external iliac artery was pulled home the femoral artery immediately collapsed, but after 15 minutes had passed it again became distended with blood flowing into it by way of the now obviously dilated deep circumflex iliac and epigastric arteries. In other words, in this short space of time the flow of blood in these arteries had completely reversed itself and was flowing from their capillary beds in the opposite direction into the deep circumflex and epigastric vessels, into the distal portion of the external iliac, and into the femoral arteries. This observation was confirmed by a needle prick of the femoral artery which bled readily but not so vigorously as it normally would. The explanation for the selection by the blood flow of the capillaries associated with the deep epigastric and circumflex iliac arteries, instead of proceeding as it does ordinarily into their accompanying venous channels, lies probably in pressure differences. The pressure immediately after ligation of the external iliac artery was zero in the arterial tree distal to the ligature. In the veins, however, the pressure was higher because the deep epigastric and circumflex iliac veins were tributaries of the portion of the external iliac vein forming a part of the aneurysm between the permanent ligatures. Therefore the patency of the veins and the intravenous pressure were maintained by the blood trapped in the ligated venous side of the aneurysm. The maintenance of the venous pressure forced the blood to the lower area of pressure in the artery and very soon reestablished the arterial circulation. An explanation is thus afforded for the beneficial

effects of ligature of the accompanying vein when ligating the artery. Numerous experimental and clinical observations have been accumulated to prove the wisdom of this procedure but heretofore the explanation of the modus operandi of this beneficial venous stasis has not been set forth. The incision was closed according to the usual manner

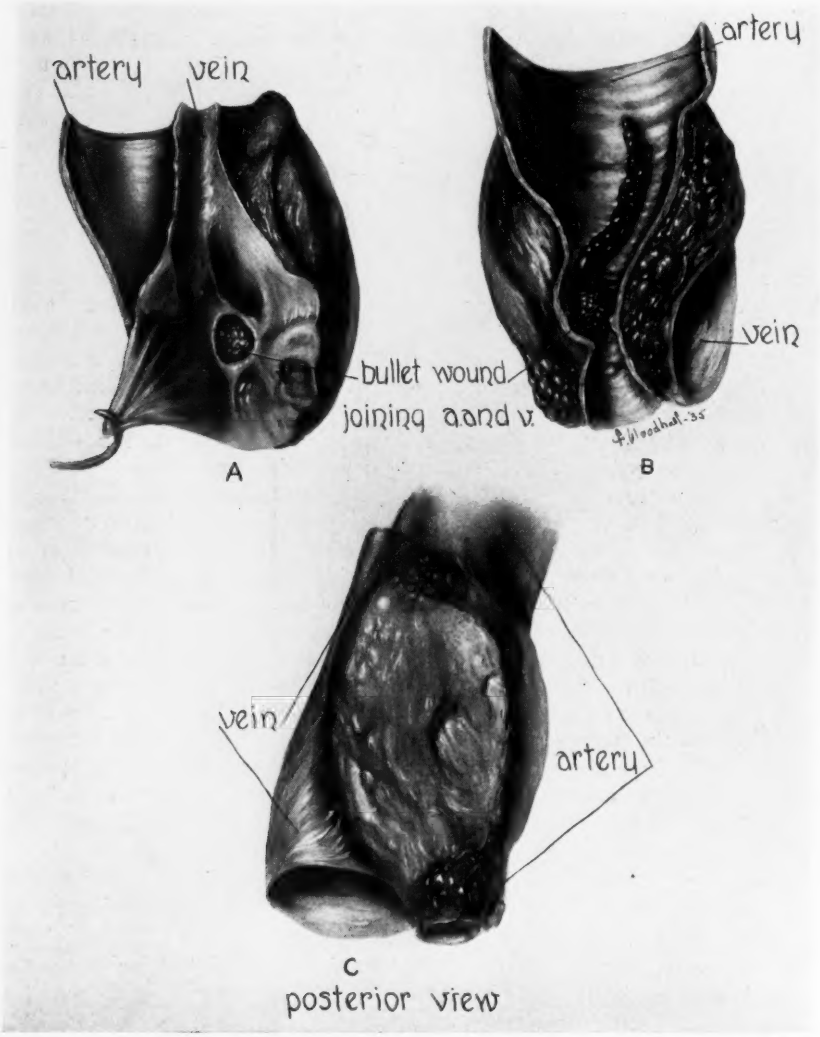

FIG. 3.—Drawings of specimen. (A) Venous side of arterial venous aneurysm showing vegetation in the opening between the external iliac vein and aneurysmal sac. The upper or proximal portion of the vein has been cut across on the bias so as to give the false impression that the lumen of the vein is narrowed in this drawing. (B) Arterial side of specimen revealing the openings into aneurysmal cavity filled with vegetations and the protruding thrombus which points cephalward. Dilated proximal portion of artery shows in upper portion of illustration. The external iliac artery of normal size is shown below. Along the right margin of the artery is the dark calcified wall of the aneurysm. The external iliac vein is on the opposite side lying directly behind the artery. (C) Posterior view of the encysted varicose aneurysm.

without drainage, *i.e.*, the posterior and anterior peritoneum were closed with a continuous suture of fine silk; the anterior sheath of the rectus muscle and skin with interrupted fine silk sutures. The operation required five and one-half hours but the patient, having lost very little blood, was not in the least shocked.

Pathologic Examination: Gross.—The specimen removed at operation measured 8.5 cm. in length and consisted of a portion of the external iliac artery and vein, a portion of the common iliac vein, and surrounding connective tissue and fat. Attached firmly to the posterior lateral surface was an oval calcified mass measuring 6×3.5×2.5 cm. The vessels were opened along their anterior surfaces and it was then seen that there was a communicating channel between them and the aneurysmal sac situated about 2.5 cm. from the lower end of the specimen (Fig. 3). The opening in the artery and in the vein was one centimeter in diameter. These openings communicated with the calcified, oval chamber so that the blood passed from the artery into the aneurysmal sac and then into the vein. This type of abnormal arteriovenous communication should be termed an encysted arteriovenous aneurysm. In addition to the above described apertures in the vessel walls there was an additional opening between the artery and vein about six centimeters in length which was in reality almost continuous with the smaller opening. Protruding from the cavity of the aneurysmal sac was a thrombus attached to the arterial wall which pointed

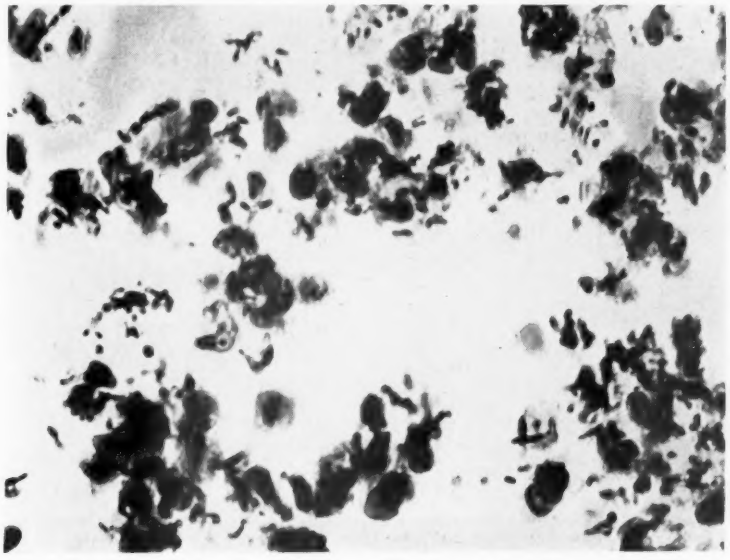

FIG. 4.—Photomicrograph of a section of the vegetations partially occluding the opening between the artery and aneurysmal sac stained to demonstrate bacteria. Many chains of streptococci are present.

cephalward in the artery, probably as a result of eddying currents above the point of the fistulous opening where the artery was constricted (Fig. 3). The walls of the vessels were markedly thickened about the opening. The lumen of the openings into the aneurysmal sac were almost completely occluded by an uneven mass of friable, yellowish-gray material, in appearance quite like the vegetations of bacterial endocarditis.

Microscopic Pathology.—The wall of the artery and vein showed much chronic inflammatory tissue between them. A large channel lined with endothelium connected the two. This channel was filled with an irregular mass of thrombus which at one point showed some organization, but, for the most part, was fairly fresh. It was attached to the wall of the channel on both sides. Scattered through this thrombus were a great many polymorphonuclear cells and groups of large, rather poorly preserved, mononuclear cells filled with great swarms of gram-positive cocci in short chains and surrounded by them (Fig. 4). No bacteria were seen in the tissue.

Postoperative Course.—After the wound had been dressed it was apparent that the circulation in the right leg was defective, as the skin was cold and mottled by areas of

cyanosis. During the operation the leg had been elevated above the level of the heart. The patient was adjusted in the recovery bed so that the leg was held level with the heart and was surrounded with hot water bottles. At the end of an hour the circulation had improved greatly and the temperature of the skin had risen to a point a little above normal. The color of the skin was then a bright pink and the areas of cyanosis had disappeared. It is interesting to note what a profound effect even slight changes in hydrostatic pressure may have upon the circulation of an extremity when the circulation is impaired.

When the patient reached the ward the temperature was 96°, the pulse 160, respirations 48, blood pressure systolic 98, diastolic 74. During the afternoon the pulse rate fell to 130. The following day the patient was much better. The pulse rate varied from 120 to 140. The blood pressure had risen to systolic 128, diastolic 86. The color of the skin had changed gradually from a vivid pink to normal. For a few days there was a little edema of the right ankle but this disappeared as the flushing of the skin subsided. It is possible that cutting the sympathetic nerve fibers about the wall of the external iliac artery

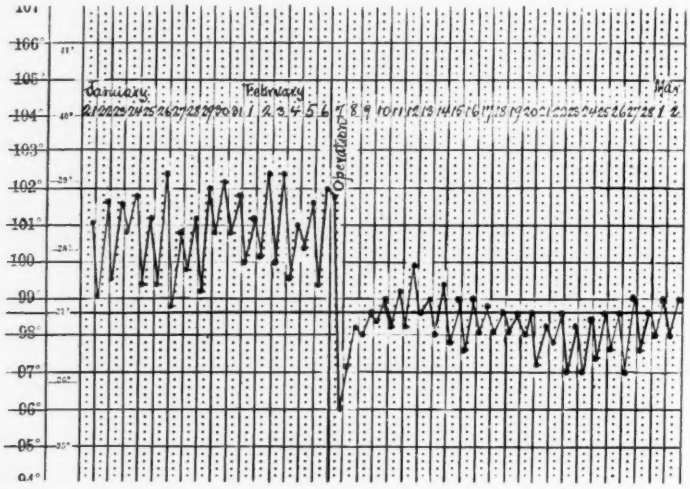

FIG. 5.—Condensed temperature chart, showing the maximum and minimum temperature each day before and after operation. The temperature, varying from 99° to 102.4°, fell to subnormal on the day of operation and after a slight postoperative rise settled permanently to the normal level.

may have caused temporary dilatation of the arterioles in the right leg and in this way accounted for the bright pink color of the skin and the edema. We may assume that as vascular tone returned the color of the skin became normal and the edema disappeared. The variation of the temperature of the skin coincided with changes in color; when the skin was bright pink the temperature was elevated, as the skin assumed a normal appearance the temperature returned to normal. Although the circulation in the right leg was quite adequate to nourish the leg satisfactorily still no pulsation could be felt in any of the arteries and the blood pressure could not be determined.

From then on the patient's recovery was uneventful. The temperature, as shown in the chart, fell to subnormal following the operation and thereafter was never raised but a little above normal (Fig. 5). The patient left the hospital in good condition on March 9, 1935. He had gained in weight. The blood count was at that time practically normal, namely, hemoglobin 85 per cent; red blood cells 4,400,000; leukocytes 6,600. The blood pressure in the arm was systolic 130, diastolic 95. The edge of the liver could still be felt at the costal margin on deep inspiration but the spleen was no longer palpable. Blood cultures were taken two hours after the operation, again during the evening of the same day and on each of the succeeding six days. All of these cultures remained sterile.

Follow Up.—A letter from Doctor Caravati dated April 24, 1935, described the patient's condition as follows: "I am pleased to report that Mr. W. has steadily improved. He is walking about without help and gaining weight steadily. There remains a slight edema of the right foot. He has been constantly afebrile. His pulse now ranges from 75 to 85. No pulsation has returned in the right leg. The liver and spleen are no longer palpable. His blood count is now practically normal. Two blood cultures have remained negative."

On May 31, 1935, the patient came to Baltimore for a final examination. He had gained 40 pounds in weight, had an excellent color and was a picture of robust health. He had been working steadily for a month, at first for half a day but during the previous week for seven hours. He walked about without any support and complained only of a little pain in the leg if he walked too far. At the end of the day there was a little swelling about the ankle which disappeared during the night. The pulse was 76. The right leg was normal in appearance. The right thigh and calf measured one centimeter more than the left. No pulsation could be felt in the right femoral artery nor in any other arteries of the leg.

CONCLUSIONS

We believe that this patient has been cured of *Streptococcus viridans* septicemia by surgical removal of the focus of infection. Certain interesting circulatory phenomena have been observed and described.

THE TREATMENT OF CAROTID CAVERNOUS ARTERIOVENOUS ANEURYSMS

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THIS report is based upon eight cases of carotid cavernous arteriovenous aneurysms treated surgically. Perhaps this condition is better known as pulsating exophthalmos, a term, however, that is less correct because it connotes a symptom rather than the underlying cause; pulsating exophthalmos results from other causes.

Arteriovenous aneurysms of this type are more common than arteriovenous aneurysms in any other part of the body. In fact, I think they occur with greater frequency than all arteriovenous aneurysms combined. There are now reports of over 800 in the literature. When one considers the anatomy of this region, it is not difficult to understand. There are vascular factors that are entirely different from those in any other part of the body. It is, I think, the only location in which an artery actually passes through a venous channel and that accounts, as does also the situation of the lesion, for the high frequency of these aneurysms.

For the production of an arteriovenous fistula in the arm, leg or neck, it is, of course, necessary to have a perforating wound, if the aneurysm is of traumatic origin, which penetrates the walls of both the artery and the contiguous vein. That is not necessary in the case of a carotid cavernous fistula because the arterial wall forms in large part the wall of the venous sinus so that only a tear in the carotid artery, where it traverses the cavernous sinus, is necessary for the production of a fistula.

About three fourths of these fistulae are of traumatic origin, and as so many of the lines of fissure traverse the middle fossa of the skull, it is easy to understand why trauma has such an important bearing on the production of this lesion.

In the other or spontaneous group, the aneurysms, though fundamentally the same anatomically, are due to rupture of latent congenital or acquired aneurysms of the carotid artery or to arteriosclerotic patches in its wall.

Little need be said about the clinical syndrome which is sharply defined and unmistakable. There is (1) exophthalmos, (2) pulsation of the protruding eye, and in the temporal region, (3) a subjective roar which to the observer is a systolic murmur on auscultation.

The treatment of these aneurysms has been most varied. In general it has been along two lines, either from the arterial side, or from the venous side. I have had no experience with the venous side, although good results have been reported.

On the arterial side, the favorite treatment has been total occlusion of either the common or internal carotid artery on the side of the lesion. How-

ever, just as good results have now been obtained by partial ligation of either of these vessels. In fact, when one analyzes the after-effects of either partial or total ligations, the results are found to be most capricious. The aneurysms may be cured very easily, or there may be no benefit whatever. In five of our cases a cure resulted soon after ligation of the internal carotid artery (one partial and four total occlusions). In three cases there was no improvement, but in one of these a spontaneous cure resulted five years later—too late for preservation of vision.

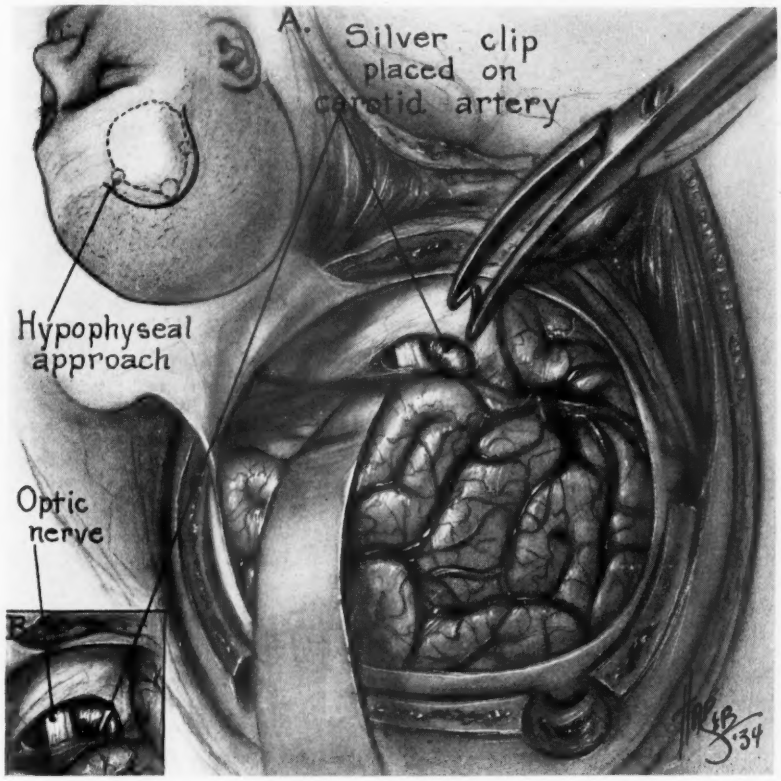

FIG. 1.—Drawing to show the method of application of a silver clip to the internal carotid artery as it enters the cranial chamber. Lower inset shows the closed clip in place on the artery which it totally occludes. Upper inset.—The heavy curved line shows the incision which is entirely behind the hair line. The dotted line indicates the position and relative size of the bone flap.

When one analyzes the results, it is quite clear that neither the cures nor failures are dependent upon isolation of the aneurysm by occlusion of the carotid, but upon the development of a thrombus in some part of the vascular apparatus, *i.e.*, in the fistula itself, the carotid artery or venous tributaries which, of course, are principally those of the ophthalmic vein.

When the internal carotid is tied in the neck there is always immediate improvement including cessation of the roar, but in 24 hours or less all signs and symptoms have usually returned, though in modified degree, later gradu-

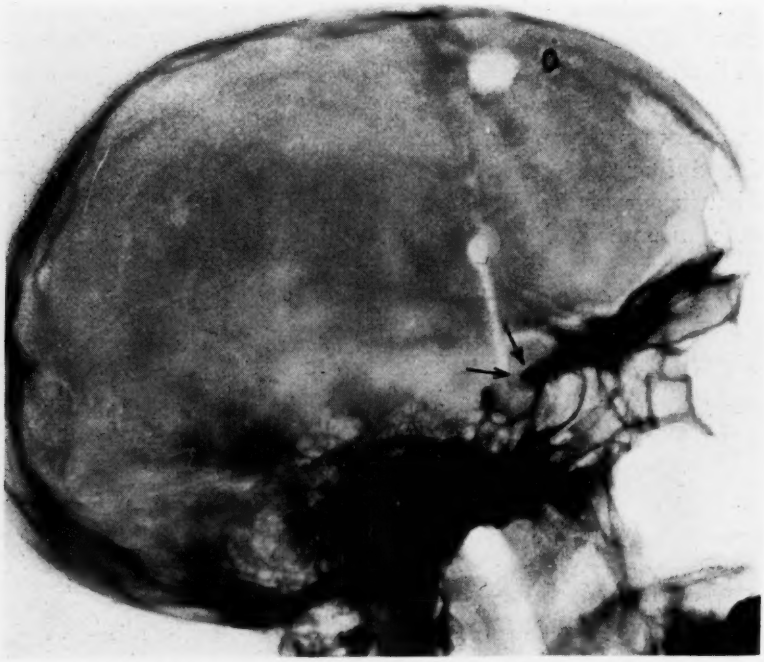

FIG. 2.—Roentgenogram showing the clip that has been placed on the internal carotid artery intracranially.

(A) (B)

FIG. 3.—(A) Patient with unilateral carotid cavernous aneurysm, before operation. (B) Same patient two weeks after the internal carotid artery has been "clipped" intracranially. This vessel had been previously ligated in the neck.

ally increasing. Whether or not there is some permanent improvement or no change depends upon whether or not thrombosis begins during the period of reduced intracranial pressure.

FIG. 4.—(A and B) Two preoperative views of a patient with a right carotid cavernous aneurysm that arose spontaneously.

FIG. 5.—Same patient three months after operation in which the internal carotid artery was closed intracranially by a silver clip. The photograph on the left shows the scar of both the cervical and intracranial ligations, between which the aneurysm was "trapped."

I am mainly concerned with the treatment of those patients who have not been cured by the arterial ligations, whether partial or total. The procedure

that I wish to present is the placement of a silver clip upon the intracranial portion of the internal carotid artery just before it divides (Figs. 1 and 2). It has been employed in two cases (Figs. 3, 4, and 5). The object of this attack is to isolate the aneurysm. This is not strictly correct because there is one sizable branch, namely, the ophthalmic artery between the point of the earlier ligation in the neck and the one intracranially. In one case this branch has had no effect upon maintaining the fistula which was cured immediately. In the other case it was almost a complete cure with complete return of the eyeball to normal, but a slight murmur persisted. It was necessary to excise most of the collateral branches entering the ophthalmic artery (*i.e.*, the branches of the external carotid artery) to complete the cure. In desperation these cases have not infrequently been treated by ligation of the internal or common carotid arteries bilaterally and with a very high incidence of disastrous results.

The exact treatment which one should use depends, of course, upon whether or not the carotid artery can be sacrified without cerebral disturbances. The physiologic test—compression of this artery with the thumb—should always be made beforehand in order to determine the exact type of ligation to be used. This test has long been emphasized as a necessary prerequisite by Doctor Matas. Roughly the age of the individual is a fairly reliable guide in determining the safety or danger of total ligation, but there are too many exceptions to permit ligation without the compression test. In an elderly person one could only partially ligate the internal or common carotid artery. When partial occlusion is advisable, I prefer the internal carotid and with a band of fascia. To reduce its size one half is safe in elderly persons, and in one of our bilateral cases this was immediately and completely effective. Total arterial occlusion is permissible only when the collateral circulation is known to be adequate. Intracranial ligation of the internal carotid artery is advocated only when all the other arterial ligations have failed to cure.

Discussion.—Dr. Rudolph Matas (New Orleans, La.).—Doctor Dandy has given us another striking illustration of the originality, skill and boldness with which he has successfully attacked many of the difficult problems in brain surgery. In this instance he has added another technical achievement to the long list of innovations and advances that are so characteristic of his surgical enterprise. His successful intracranial occlusion of the internal carotid for the relief of pulsating exophthalmos is unique and probably the most aggressive performance thus far recorded for the cure of this dangerous and elusive vascular lesion.

Doctor Dandy's procedure, as I understand it, is to occlude the internal carotid with a metallic (silver) clip, at its exit from the cavernous sinus just below its division into its cerebral and posterior communicating branches. The purpose of the operation is to obliterate the abnormal communication or fistula existing between the internal carotid and the cavernous sinus by arresting the arterial flow on the distal side of the fistula, on the principle of a Brasdor ligation. This would cause a stasis which would favor the development of an obstructive thrombus in the fistula or secondary ob-

structive changes in the artery itself. It is presumed that by occluding the artery intracranially on the distal side, but close to the fistula, the chances of obliteration would be greater than by ligating the artery extracranially, on the proximal side, but at a distance, in the neck.

There are two places in which, theoretically at least, a clip may be applied to the internal carotid within the cranium. The first, in its free portion after its exit from the cavernous sinus, is relatively simple; the second, at its entrance into the cavernous sinus after leaving the carotid canal, where it lies hidden under its dural cover in the parasellar groove. This is anatomically feasible but surgically prohibitive. A clip applied to the carotid in its free portion, after its exit from the cavernous sinus and after it has given origin to the ophthalmic artery, misses the arteriovenous fistula altogether, as this lies in the sinus below the clip. The only real advantage of the clip on the carotid at this level is that it blocks an immediate downward (reversed) flow from the circle of Willis into the fistula. On the other hand, it does not prevent a free flow from the internal carotid into the fistula, as it enters the proximal or cardiac side of the sinus. According to all experience, a clip applied to the carotid on the proximal side of the fistula as this enters the cavernous sinus in the parasellar groove would be more effective than a distal occlusion, just as a proximal ligation on the Anel principle is far more effective for the cure of aneurysm than a distal Brasdor ligation. A mere glance at the anatomic relations of the internal carotid as it lies in the parasellar groove will suffice to show how hazardous such a procedure would be, even though we imagined it to be feasible in vivo with the brain in situ. To expose the artery in the middle fossa as it lies in the parasellar groove would necessitate an incision through its dural cover and the opening of the cavernous sinus. Apart from the profuse arteriovenous hemorrhage that would follow, the sixth nerve which closely hugs the artery here would be unavoidably injured, with scarcely less narrow escape of the other cranial nerves from the third to the sixth, if the clip were placed on the artery in the cavernous sinus anywhere near the middle or anterior clinoid processes. This, however, is an idle conjecture since it is evident that Doctor Dandy contemplated no such enterprise. He confines his intervention to the distal occlusion of the artery in its free portion at its exit from the cavernous sinus. In order to do this, he opens the skull by way of his well known frontal approach to the hypophysis through a trap-door osteoplastic and dural flap. The anterior lobe is then lifted and the artery is exposed and clamped as it emerges from the sinus between the optic nerve and the motor oculi communis. To do this, as he has done twice successfully, is a fine surgical feat; but it involves, none the less, a severe cranial and endocranial trauma, and adds the dangers that are common to all intracranial operations, without in the least avoiding the risks of cerebral ischemia that are inherent to all the ligations of the common and internal carotid tracts.[1] * This technic may be simple and its risks perhaps negligible in the hands of such a consummate master of brain surgery as Doctor Dandy, but even so it is a question whether the benefits or possible advantages of such a procedure compensate for the risks involved in its performance. Doctor Dandy, however, frankly admits that his operation is not to be resorted to as a primary procedure, or as a method of election, and only after carotid ligations or other less dangerous and less delicate extracranial methods have failed. But, apart from the

* This and following reference numbers refer to supplementary notes at the end of this discussion.

purely technical aspects of the operation, may we ask, does the intracranial occlusion of the internal carotid, on the distal side of the fistula, offer a greater certainty of cure and protection from relapse that would make it preferable to the methods that are still available when the classic carotid ligations in the neck have failed and relapse has occurred?[2]

In considering the question of relapse, we should remember that the free anastomoses that exist between the internal and external carotid systems through the circle of Willis on the one hand, and, on the other, through the orbital branches of the ophthalmic artery with the ophthalmic on the opposite side, and with orbital, facial, temporal and meningeal branches of the external carotid, it is always possible for the arterial current to feed the fistula as long as this is not absolutely closed.

Since it is not practicable or even justifiable to attempt the direct occlusion of the fistula by attacking it in the orbit or in the sinus, *i.e., in loco lesionis*, except in advanced cases in which the visual function is lost or permanently impaired, and the saving of the eye becomes a minor consideration—practically all the methods of cure now in vogue aim at the thrombotic occlusion of the fistula indirectly by suppressing or reducing the arterial (carotid) supply to the fistula, or favoring thrombosis by sclerogenic injections on the venous side.

If the thrombotic plug is effective and it organizes into a scar, the fistula is obliterated and the cure, as a rule, is complete, in so far as the gross objective effects of the fistula are concerned. This happens probably in from 40 to 50 per cent of the cases reported as "cured" by carotid ligations alone or combined with other methods of treatment which tend to favor thrombosis in the sinus or in the ophthalmic veins, and indirectly in the fistula itself.[3]

In a large proportion of cases reported as "improved" (from 40 to 50 per cent), the thrombotic occlusion is only partial, and the relief will depend largely upon the extent of the occlusion. In the great majority, symptomatic relief will be experienced after a carotid ligation; the exophthalmos will recede, vision will be improved, pulsation will cease perceptibly, and the exasperating endocranial bruits will become so subdued as to be quite tolerable. In these cases the relief may be progressive and permanent, and a symptomatic cure will be effected. Judging by my own experience and by a careful scanning of a great number of the reported cures in the literature, I find that in cases in which the exophthalmos, with large pulsating orbital and peri-orbital veins, has figured prominently, the "cure" is only relative and not absolute, as a complete *restitutio ab integro* very exceptionally occurs.[4]

In a considerable number of these reported cases (20 to 30 per cent), after a temporary improvement, which may last from a few hours to two or three years, relapse occurs, varying in time with the persistence of the fistula and the development of the collateral circulation. The exophthalmos then returns with all its aggravating subjective and objective features, visual defects, disturbances and frequent extension to the other eye. The patient is then driven to desperation and the surgeon compelled to adopt more drastic treatments.

Since the new procedure advocated by Doctor Dandy does not aim at a direct obliteration of the fistula, and only indirectly by temporarily reducing or suppressing the carotid circulation on its distal side, it enters into the class of indirect cures by carotid ligation, and it can give no positive assurance of cure, no more than the proximal carotid ligation in the neck. While recognizing that the chances of cure by clotting the fistula may be improved by this procedure in cases in which the carotids have been previously

ligated—because the fistula is then caught between a proximal and distal obstacle put in the course of its arterial supply—it does not follow that such must be the result of the intervention. We should remember that in the relapsed or rebellious cases for which Doctor Dandy has devised his operation the collateral circulation by anastomotic routes between the external and internal carotid systems has had time to develop and become freely reestablished through the fistula. It would seem that, under these conditions, the arterial supply of the fistula will not be so materially checked, even though the reflux coming from the distal side through the circle of Willis has been cut off.

In view, therefore, of what has been said, I would conclude that the intracranial occlusion of the internal carotid on the distal side of the fistula can offer no better chances of cure as a primary or initial procedure than by the extracranial carotid ligations in the neck, in which I believe Doctor Dandy agrees. It is only when the proximal carotid supply has been cut off by a previous ligation in the neck that the intracranial operation has a better chance of proving effectual. That is, provided the collateral circulation coming from the circle of Willis through the opposite ophthalmic artery and the intraorbital anastomosis of the external carotid has not developed sufficiently to nullify or counterbalance its obliterative thrombogenic effect.

The two recent operations successfully performed by Doctor Dandy redound greatly to his credit and are perhaps the strongest argument in favor of his method, but, much as I admire his originality, his great skill and the boldness of his enterprise, I regret to say that the problem of pulsating exophthalmos has not yet been definitely solved by his experience.

The evidence of Doctor Dandy's success, furnished by his two recent operations, is sufficient to demonstrate the surgical feasibility of his procedure, but not sufficient to prove that it offers greater certainty of cure or protection against relapse, than the less brilliant but safer and more direct methods of treatment that are still available, with as much claim to success, in the same class of cases.

SUPPLEMENTARY NOTES

(1) In my personal experience with 80 ligations or band occlusions of the common and internal carotids we have had nine cases, or 11.2 per cent, in which grave cerebral complications have occurred, and of these six, or 7.5 per cent, died. Three others were saved by the timely removal of the aluminum bands which I use for this purpose. The most striking of these rescues from cerebral death was in an exophthalmos patient who, after he had been saved by the prompt removal of the band, was able to undergo a second occlusion two years after the first attempt, without any notable ill effects, after a four weeks' course of systematic and methodical compression of the common carotid in the neck. The patient was symptomatically cured, and reported himself "entirely well" three years after the operation; but a photograph enclosed in his letter showed that the proptosis still lingered sufficiently to give a slight but distinctive feature to his face. (Matas, J.A.M.A., October 24, 1914).

(2) The problem of pulsating exophthalmos has been attacked surgically in at least five different directions:

(*a*) On the arterial side by the carotid route. *Extracranially,* in at least nine different ways, including digital and mechanical compression; partial occlusion; ligation of the common and internal carotids and their branches, singly or in different combinations; by the consecutive ligation of both common carotids in relapsed cases; *Intracranially,* by occlusion of the internal carotid (Dandy's operation).

(*b*) On the arterial side, by plugging the fistula itself, with muscle tissue, by way of the internal carotid (Brooks); by plugging the fistula with paraffin injected into the internal carotid at its origin in the neck (Dawborn-Matas).

(*c*) On the venous side: (1) by extirpation of the ophthalmic veins through the orbit; (2) electrocoagulation of the veins by diathermy (Fiolatox) extending as far as the sinus; (3) by injecting the veins with sclerogenic solutions.

(*d*) By direct attack on the fistula at the apex of the orbit, with evacuation of the orbital contents, in cases in which vision is lost and the enucleation of the eye is of minor importance.

(*e*) By constitutional treatment to increase coagulability of the blood by diet, gelatin injections and other means.

All these methods, whether singly or in combination, claim a share of the successful statistics, except those in Group 2, which are thus far purely theoretical and experimental. Thus far, the arterial attack by compression, and the extracranial ligation of the carotids, retains the supremacy that it has held since Travers, 130 years ago. The venous route, by way of sclerogenic injections, has not been sufficiently exploited in the modern sense. The direct attack on the fistula at the apex of the orbit, with or without evacuation of orbits, remains a supreme resource in old relapsed and inveterate cases in which vision has been lost. Accidental, or spontaneous acute thrombophlebitis, as an intercurrent complication, has proved, in the author's experience, the most effective, complete and radical cure of exophthalmos in the relapsed (ligated) cases.

(3) According to Locke, in his thorough analysis of 588 reported cases of pulsating exophthalmos during the period 1809–1923 (ANNALS OF SURGERY, vol. 80, July, 1924), 272 ligations of the common and internal carotids yielded 187 (68.75 per cent) "cured" or "improved" by these ligations. These ligations do not include 21 bilateral consecutive carotid ligations in relapsed cases, with 61.91 per cent cures, nor 24 primary carotid ligations combined with orbital vein ligations, with 37.50 cures, and 33.33 per cent improvements.

(4) The term "cure" simply means that the abnormal arteriovenous flow through the fistula has been checked, but the effects of the arteriovenous lesion on the contents of the orbit, the eye, and the veins of the orbit, persist in long standing and especially bilateral cases, as tell-tale relics of the previous existence of the exophthalmic disorder. I dare say that in the majority of the reported "cures" faint murmurs will be heard with the stethoscope and by the patient himself, if he listens intently with his head on a pillow in the stillness of the night. Travers' now historic case of first carotid ligation for exophthalmos still showed signs of the old disfiguring disorder, which could not escape detection by even an inexperienced eye, seven years after an apparent symptomatic cure had been accomplished by the ligation. In this connection I would say that the most complete and radical cures that I have known are those which have followed the obliterating effect of an acute, spontaneous thrombophlebitis. We have had four such cases, in three after failure of carotid ligations. It is this experience that has convinced me of the neglected advantage of attacking a rebellious exophthalmos by combining the carotid ligation with mild obliterating sclerogenic injections (*e.g.*, 50 per cent dextrose or crystallose) into the ophthalmic veins, and in this way inducing a relatively benign thrombophlebitis in imitation of Nature's mode of cure.

DR. HOWARD C. NAFFZIGER (San Francisco, Cal.).—I understand from Doctor Dandy that the clipping of the carotid is, of course, distal to the origin of the ophthalmic artery, and I understand that there has been no subsequent difficulty with vision. I should think that visual disturbances would be common following the ligation of the carotid artery in this location and that collateral circulation would be inadequate, and have been fearful of an intracranial tie for that reason.

We have had about 15 of these patients. Doctor Locke reported a number some years ago. Our experience has been the same as that of others, namely, that the most satisfactory results are found in those patients who have spontaneous healing. We followed the progress of one patient, who had no treatment, for 10 or 15 years. His bruit remained the same and there was no change in his eye. A comparison of his progress with that of patients who had had the internal carotid tied showed very little difference.

We have banded and tied the common carotid, but more frequently the internal carotid.

In the treatment of these patients we have noted that the frequent digital compression of the common carotid artery is helpful. This, however, is a tiresome procedure and cannot always be continued for as long a period as is desirable. One of our patients used a trouser clip—the kind used to hold the trousers away from the chain of a bicycle—which has proved to be a most effective piece of apparatus.

The pathologic change in this condition is, in my opinion, a relatively slow process rather than a tear. I think that there is a latent period of from two to three weeks in which the bruised wall of the artery becomes progressively weaker and finally ruptures. In the literature, as I recall, the average time of the appearance of symptoms after injury is given as about 21 days. In our cases the symptoms usually have appeared between two and three weeks after injury.

In connection with Doctor Dandy's procedure, I should like to ask particularly about the circulation in the ophthalmic artery, as that would be a cause for worry.

DR. MONT R. REID (Cincinnati, Ohio).—I think Doctor Dandy has made his point perfectly clear that he would not resort to this method until all other procedures had failed. One or two things might be stressed regarding the procedures which should be tried before resorting to intracranial manipulations.

It is extremely important to pay attention to the possible collateral circulation through the external carotid artery. If one should elect to ligate the common carotid artery alone there will be a reversal of the flow of blood in the external carotid back into the internal carotid and thence on to the brain. Consequently, if one ligates the common carotid artery the external carotid should also be ligated, in order to reduce to the maximum amount the arterial circulation through the fistula. It may also be true that if one ligates the internal carotid one can further reduce the arterial circulation through the fistula by ligating the external carotid which anastomoses with branches of the ophthalmic artery. My practice has been to occlude the common carotid artery with a metallic band, which can be removed later if necessary, and at the same time to ligate the external carotid.

I think it is advisable to attack the venous side if the arterial ligations in the neck fail to cure the fistula. As deSchweinitz pointed out a good many years ago, many of these cases have been cured by simple ligation of the supra-orbital vein and this might be done after the arterial ligations. It seems to me we may do more than ligate the vein. It might be possible to open it and to introduce some sclerosing solution back toward the cavernous sinus and thus promote thrombosis. In one of our cases we have opened the supra-orbital vein and tried to introduce into it a little flexible probe, something like a miniature test tube cleaner, after dipping it into 50 per cent glucose solution. I simply bring out those points as possibly worth trying before resorting to the intracranial approach.

One other point: we believe that the older patients are, the less likelihood there is of cerebral disturbance following ligation of the carotid artery. I do not know the explanation for this, unless the cerebral vessels become more or less rigid later on in life and are not subject to collapse of their walls and to the vasomotor spasms that you get in younger people. Certainly our experience has been that it is safer to ligate the carotid vessels in older people than in young people.

Dr. Walter E. Dandy (Baltimore, Md.).—It has been our thought in this procedure that perhaps the aneurysm might be isolated and the cure might not require thrombosis. There is, of course, one sizeable branch—the ophthalmic artery—between the intracranial and the cervical ligatures.

In answering Doctor Naffziger's query, concerning the danger to vision by so isolating the ophthalmic artery, I can only say that in neither of the two cases was there any postoperative loss. This was indeed our greatest concern, and both patients were warned that blindness of the affected eye might result. As they came out of the anesthetic the pupil on the side of the ligation was widely dilated, but when fully awake toward evening the vision was perfectly normal.

Since the collateral circulation from the branches of the external carotid artery has maintained the circulation to the eye, it may well be that the same circulation will maintain the aneurysm, though at a reduced pace, until thrombosis completes the cure.

The results from deep intra-orbital ligations of the huge ophthalmic vein have been published by deSchweinitz, Sattler and others. Although most of the reports are quite meager, some of the cures are no less perfect than by the arterial ligations. Immediately following ligation of the ophthalmic vein there is always an acute alarming intensification of the exophthalmus and chemosis. This change is due to the strain thrown upon the remaining venous channels in the orbit after the sudden removal of the big venous bed through which the arterial blood has been making its exit.

Then too, I have been fearful of ligating the ophthalmic vessels deeply in the orbit because of the danger of injuring the extra-ocular muscles or their nerves; a non-focusing eye is scarcely better than a blind one. I feel that the safer attack upon carotid cavernous aneurysms is through the arterial ligation, and with proper care in the procedure, *i.e.*, partial or total depending upon a preoperative determination of the collateral, there should be a minimal risk to life or function. I should like to repeat that when intracranial clipping of the carotid artery is necessary there is no risk to the circulation of the brain because the internal carotid has already been ligated in the neck.

INFLUENCE OF URINARY BLADDER TRANSPLANTS ON HYALINE CARTILAGE *

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IN VIEW of the surprising results obtained from studies of the ability of the epithelium of the dog's bladder to stimulate bone formation, it seemed desirable to observe the effect of bladder epithelium on cartilage.

A previous article reported the results of experiments in which defects in the ulnas of dogs were bridged by transplants of the mucous membrane of the urinary bladder of the same animal.[10, 11] These experiments were based upon an observation of Huggins[1, 3] who found that, if the mucous membrane of the urinary bladder of dogs was transplanted to the rectus sheath, fascia lata or subcutaneous tissue, a cyst lined by bladder epithelium was produced, and true bone was almost always formed in a part of the wall of the cyst. This is true bone in that it contains haversian canals and hematopoietic marrow, and its formation appears to be due to some influence of the proliferating cells lining the cyst or their products. Osteogenesis also followed transplantation of kidney pelvis, ureter[2, 5] and gallbladder[7] into parietal connective tissues of the abdominal wall, extremities and neck but did not occur following similar transplantation of gastric, jejunal and prostatic epithelium. The connective tissue surrounding the epithelium in the urinary tract and the fibroblasts within solid organs such as the kidney cortex, liver and spleen do not react to transplanted bladder mucosa by forming bone. The secretion of fluid in epithelial-lined cysts of the transplanted mucosa was found by Huggins and Compere[6] to contain relatively large amounts of calcium and phosphorus, as compared with the blood of the same animal, and this fact is considered a factor in the bone formation. Huggins[4] later found the phosphatase activity to be relatively high in the various stages of heterotopic osteogenesis in transplants of bladder mucosa. He[8, 9] also studied heterotopic formation of dentine and enamel by transplantation of epithelium and pulp tissue, and found the reaction similar to the production of bone by transplanted urinary tract epithelium. Other literature concerning heteroplastic formation of bone has been reviewed by Huggins.[3]

Our own experiments[11] indicated that the presence of a growing autologous transplant of epithelium from the urinary bladder of a dog stimulated osteogenesis in a defect in the ulna and caused the defect to be bridged by new bone which resulted ordinarily in union. Control defects in the other ulna of the same dog which did not have a transplant failed to unite. Examination of the specimens indicated that the new bone was formed directly under the influence

* Dr. William Ehrlich assisted in performing the experiments.

of the growing transplanted epithelium of the bladder rather than to any influence of the periosteum or of any other structure. Furthermore, the bladder transplant tended to prevent atrophy of the ends of the bone defects which uniformly occurred in the same dog on the control side with nonunion of the ulna. The new bone was usually formed directly in the connective tissue and was not preceded by the formation of cartilage.

We were unable to explain the exact mechanism by which the bladder transplant caused formation of bone. Various kinds of extracts of bladder epithelium of dogs and hogs proved to be inactive in bringing about union of experimental fractures. One extract of bladder epithelium* temporarily raised the blood calcium and lowered the blood phosphorus when given intravenously to dogs. It is possible the new bone resulted in part from a local excess of calcium or of phosphatase which was secreted by the epithelial cells of the transplant.

METHOD.—To investigate the effect of the mucous membrane of the urinary bladder on cartilage, surgical operations were performed aseptically on 12 dogs under ether anesthesia. It was thought desirable to use hyaline cartilage for the experiments since it is the most primitive and most widely distributed type, and is readily available in costal cartilages. The operative procedure follows:

Sections of either the eighth, ninth, tenth or eleventh costal cartilages averaging from 2 to 3 cm. in length were resected subperichondrially on each side of the chest. In some of the animals the perichondrium was poorly developed. The urinary bladder was exposed and a piece of the entire wall of the bladder approximately 3 cm. square was excised. The bladder wound was sutured and the abdominal wall was closed. The mucous membrane was dissected carefully from the muscularis of the piece of the wall that had been excised. The isolated epithelial layer is of tissue paper thinness and texture. The small strips of mucous membrane were transplanted by stretching them across the defect in the costal cartilage and by suturing them in place against the ends of the cartilaginous defect with fine silk sutures. Usually the transplants were made to the right side of the chest only, however, in a few of the animals bilateral transplants were made. The wounds were carefully closed about the transplants with interrupted silk sutures. The control side without a transplant was closed in the same manner. The animals were sacrificed at various intervals from four days to six months after operation and the anterior half of the thorax was removed en masse for roentgenologic, and for gross and microscopic study.

RESULTS.—*Gross Appearance.*—There was no difference of note in the experiments of short duration between the control side and the defect containing the bladder transplant. In the experiments of longer duration the ends of the cartilage on the control side were united by fibrous tissue. There remained slight depressions at the site from which the cartilages had been

* Made by Eli Lilly.

removed. The defects in the same animal which were bridged by bladder mucosa were usually filled by a mass of tissue consisting of bone and cysts varying in size according to the duration of the experiment. The cysts were both multiple small ones and multilocular. A false joint was always found at the site of the defect on the control side, while on the side of the transplant there tended to be some fixation of the ends of the cartilage by the mass of tissue depending upon the duration of the experiment. There was no palpable evidence of regenerated cartilage in any control specimen. On section across

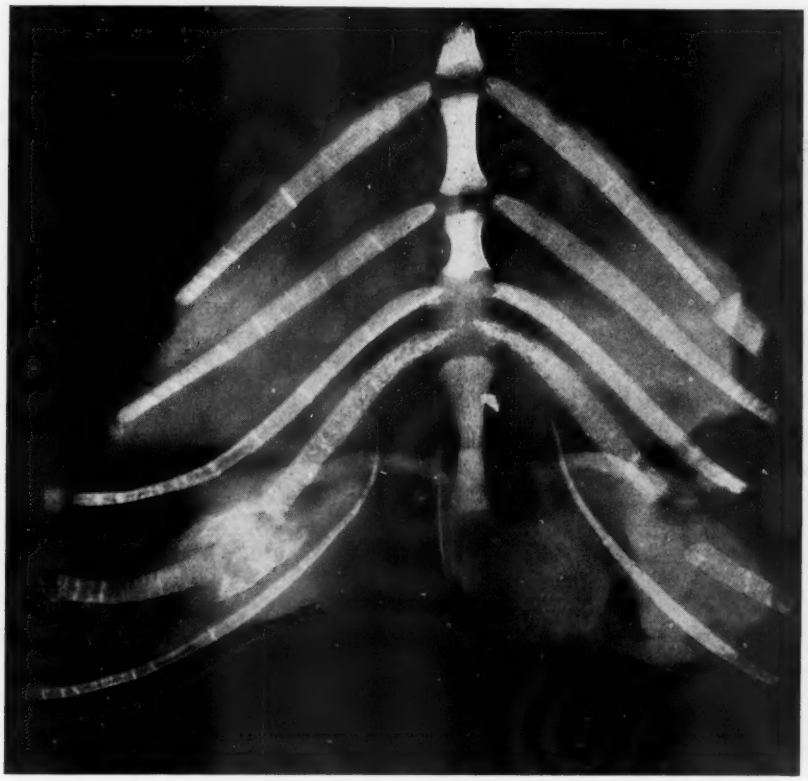

FIG. 1.—Roentgenogram of anterior portion of dog's chest. On the left side may be seen the experimental control defect in the tenth costal cartilage. The defect in the right tenth costal cartilage is filled with a cystic bony mass that resulted from an autogenous transplant of urinary bladder mucosa. The transplantation was made at the same time the defects in the cartilage were created, eight weeks previously.

the cartilaginous defect there was seen grossly a ribbon of dense but pliable fibrous tissue.

Roentgenologic Examination.—Postmortem roentgenograms of the anterior half of the thoracic wall of each dog were made. On the control side the shadow cast at the site of the defect is of no greater density than the surrounding soft tissue. The ends of the cartilage at the defect are clearly outlined and atrophic changes are little if any. This is in contrast to defects in bone as observed by roentgenograms in other experiments which showed

rarefaction, particularly of the ends of the bones, and a definite decrease in the diameter of the remaining shaft.

In the experiments of short duration with cartilage the roentgenograms of the transplant and the control sides were practically the same. As early as three weeks the defects in the cartilage that had been bridged by bladder transplants are occupied by a mass of calcified tissue several times larger than the original defect (Fig. 1). The calcified mass known to be composed largely of bone contains many clear areas of various sizes. These clear areas represent multiple cysts formed by the proliferating bladder epithelium. In the longer experiments the calcified tissue in the defects cast a denser shadow and the clear areas are not pronounced. Furthermore, some of the ends of the cartilages are rarefied and the size of the defect seems slightly increased. These latter findings give the impression that the calcified mass has replaced small portions of the cartilaginous ends of the defects. This observation has been verified by histologic sections.

Microscopic Examination.—Controls: The defects in the early experiments were filled with a mass of blood clot and granulation tissue, and the ends of the cartilage are sharply demarcated from these tissues. Throughout the length of the older defects there can be seen microscopically dense fibrous tissue (Fig. 2). The ends of the cartilage are rounded and the cartilage usually remains separated from the surrounding perichondrium. Occasionally the ends of the cartilage fuses with the perichondrium and together they join the mass of fibrous tissue filling the defect. Very rarely there may be found in a few sections interspersed in the fibrous tissue small islands of fibrocartilage, doubtless having arisen from small pieces of cartilage left attached to the perichondrium at the time of the subperichondrial resection. There is no evidence of invasion of the defect at either the sternal or costal end of the defect by proliferating cartilage or bone. The rounded ends of the cartilage are little atrophied, are not calcified, and have failed to regenerate.

BLADDER TRANSPLANTS INTO DEFECTS OF COSTAL CARTILAGE

In the seven and fourteen day experiments the defect in the hyaline cartilage is filled with an organizing blood clot containing masses of bladder epithelium in which the cells are proliferating. Many of the masses of cells have formed small cysts which occur as single, multiple and multilocular types (Fig. 3). These early cysts do not contain a material that can be fixed and stained, and they are surrounded by a layer of fine, loosely arranged and probably edematous young connective tissue. The epithelium of the cysts is transitional in type, of a hardy variety, and consists usually of a number of layers. The shapes of the cells vary but most are ovoid. The cells of the superficial layers are larger and are stained less with eosin than the deeper ones that tend to overlap each other. All phases of mitosis can be seen in the nuclei. There is no bone around the walls of the cysts at the end of two weeks. The ends of the cartilage that had been resected to make the defect are apparently viable and show no evidence of regeneration after 14 days.

The ends are rounded and covered with perichondrium which fuses with a mass of connective tissue that fills the defect.

Sections made from the 21-day-old experiment first show that the growing bladder epithelial cells have the remarkable power of producing ossification of

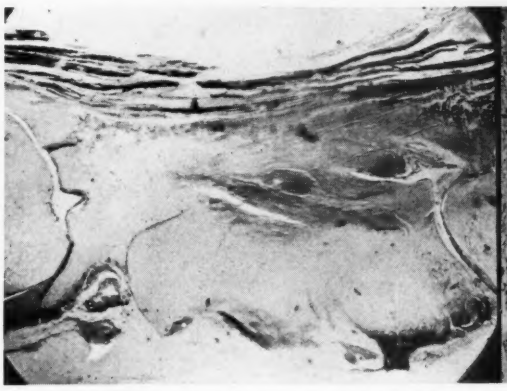

FIG. 2.—Section made through an experimental defect showing the space between the rounded cartilaginous ends to be filled with fibrous tissue.

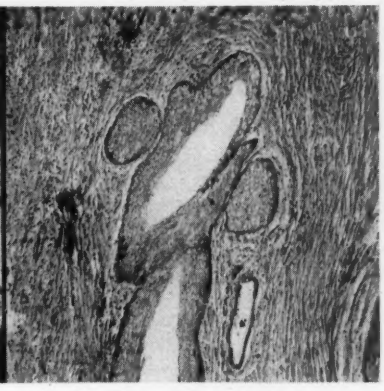

FIG. 3.—The proliferating cells of the bladder mucosa are seen to occur in masses and in small cysts two weeks after transplantation. A layer of edematous young connective tissue immediately surrounding the proliferating cells separates them from the older connective tissue.

hyaline cartilage. The epithelial cells by this time have increased in number and have become flattened as if the cyst were distended. The walls of the cysts fortunately have grown in many specimens directly in contact with hyaline cartilage and perichondrium, with only a very thin layer of loose

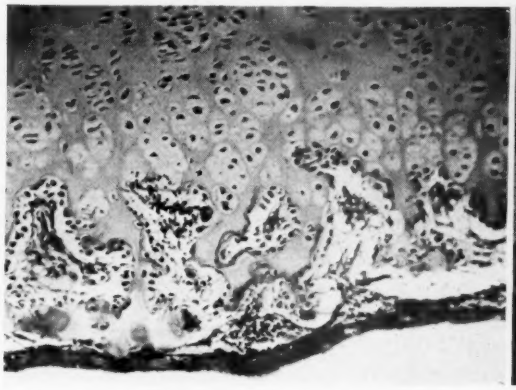

FIG. 4.—Early destructive changes have taken place in the hyaline cartilage where it is in contact with the proliferating bladder cells of a cyst. Osteogenic tissue can be seen invading the matrix and enlarged lacunae.

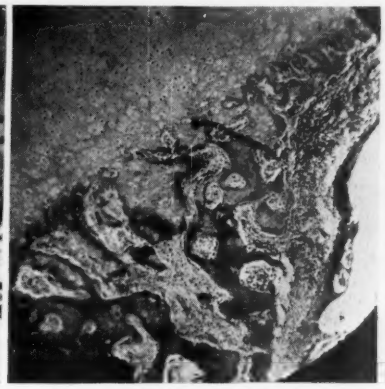

FIG. 5.—More advanced changes have occurred at the end of eight weeks in the cartilage under the influence of bladder mucosal cells. Spicules of bone are being formed in the region of the mucosa.

young connective tissue and blood vessels intervening. The structure found eventually in contact with the autotransplants and its proliferating cells is a fortuitous matter. Further, it is to be recalled that Huggins[1] found, and we confirmed his findings, that bone usually does not completely surround a

single large cyst and that it is formed always in the vicinity of the newly formed epithelium rather than the original transplant. Therefore, the chance of position plays an important rôle in determining what tissue is brought under the influence of the proliferating bladder cells. It is evident, however, from sections that the effect of growing bladder epithelium is far reaching and that it is not necessary that it be immediately adjacent to cartilage to effect it.

Under the influence of the bladder cells, the hyaline cartilage may be seen being replaced by bone and bone marrow. All phases of this transformation will be described from study of many sections made from specimens obtained from the different experiments. The 21-day-old experiment, as well as the older ones, may have present several stages of replacement of cartilage by bone, and also show the formation of bone from connective tissue and from perichondrium. In all instances the newly formed bone is lamellar bone with haversian systems and contains much bone marrow.

Marked changes in hyaline cartilage takes place early when it is in contact with growing bladder cells that form the wall of the cyst. The epithelium is separated from the cartilage by a thin layer of fibroblasts and blood vessels only (Fig. 4). Among the early changes noted are the proliferation and hypertrophy of the cartilage cells which results in greatly enlarged lacunae that often contain several cells. The enlarged cartilage cells tend to be arranged in rows, more or less parallel to the wall of the cyst and are often separated only by narrow transverse partitions. The matrix adjacent to the bladder epithelium is invaded by newly formed blood vessels and young connective tissue in which osteoblasts and primitive marrow cells are constantly differentiating. The invading osteogenetic tissue opens the enlarged lacunae, breaking the matrix into irregularly shaped septa with marrow spaces between them. The edges of the septa that project from the main body of cartilage and the particles of matrix that have been completely isolated stain more deeply than the other portions of the matrix. This fact indicates the deposition of calcium in the matrix and, as can be seen later, it is in preparation for ossification which takes place rapidly. The cartilage cells near the zones of calcification show signs of disintegration and mainly disappear early.

The osteogenetic tissue between the projections of cartilage that are undergoing calcification becomes progressively more active from month to month (Fig. 5). In addition to young connective tissue and blood vessels, there can be seen in the older specimens, young and mature forms of erythrocytes, granulocytes, lymphocytes and monocytes. Multinucleated cells are numerous and they appear often to take a prominent part in the breaking up of the cartilage. Some of the cells of the osteogenetic tissue adjacent to the cartilage in process of calcification differentiate into osteoblasts which proceed with endochondral ossification. They arrange themselves around the projections or the islands of partially or completely calcified cartilage and form layers of bone, usually enclosing cartilaginous remnants that disappear. The process of calcification proceeds simultaneously with ossification, the zone of calcification shading into a zone of ossification. The spicules of spongy bone increase in

size, particularly in length, as the osteoblasts continue to lay down more bone (Figs. 5, 6 and 7). The fibers and calcified matrix of the bone are deposited

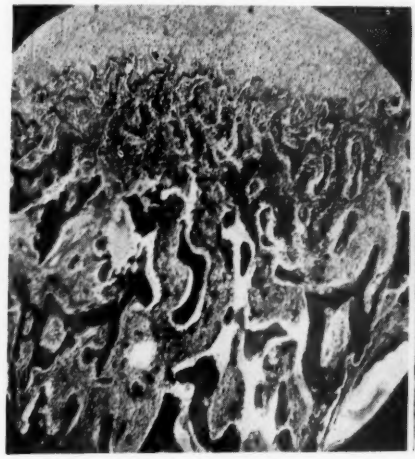

FIG. 6.—The histologic appearance 20 weeks after transplantation of bladder mucosa near cartilage resembles an ossification center in an epiphysis. The replacement of the hyaline cartilage by spongy bone can be clearly seen. Only small portions of the walls of two epithelial cysts show in the lower parts of the photomicrograph.

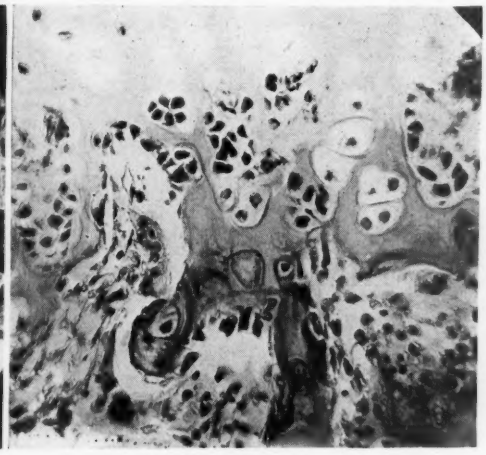

FIG. 7.—A higher magnification of the zone of cartilage in Fig. 6 which is being invaded by osteogenic tissue.

in thin layers or lamellae. The spicules of bone at the end of five months have become quite dense but the type of bone remains spongy rather than compact. The spicules tend to anastomose to form trabecula and to enclose large

FIG. 8.—A higher magnification of a portion of Fig. 6, showing trabeculae of bone surrounded by osteoblasts and mature bone marrow. In the lower portion of the view may be seen two masses of bladder cells.

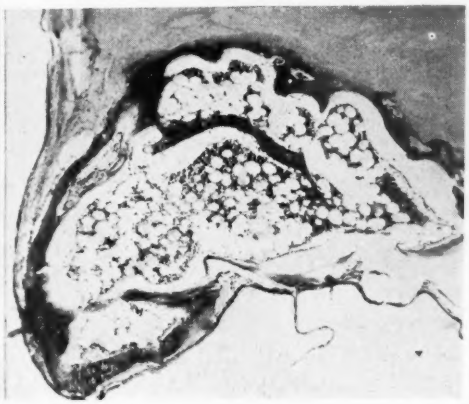

FIG. 9.—Bone is forming after three weeks in cartilage that is surrounded by an epithelial wall of a cyst. The bone is replacing the cartilage by a more direct method than the one illustrated by preceding photomicrographs. The reticular tissue of the marrow shows well.

amounts of mature marrow (Fig. 8). The bone thus formed is not destroyed by the action of osteoclasts or osteolytic agents and it shows no tendency to atrophy. Osteoclasts are comparatively rarely seen in any of the sections.

The total amount of hyaline cartilage replaced by endochondral bone formation is not large at the end of five months. The process, however, had been progressive and doubtless more cartilage would be replaced if the experiments had been allowed to continue longer.

Some of the sections showing the process of transformation of cartilage to bone that has been described, also shows less commonly a more direct method of replacing cartilage by bone. The two processes may proceed simultaneously in different regions, sometimes about the same cyst of vesical epithelium. Sections made from the 21-day-old experiment show new bone with marrow to have replaced already considerable cartilage by this different method (Fig. 9). The cartilage in the region of the bladder epithelium and at some distance from it has been stained pink with eosin, indicating probably that some calcification of the matrix has taken place. The lacunae are evenly

FIG. 10.—Higher magnification of a bone-forming zone of Fig. 9. The collagenous fibers can be seen among the cartilage cells and calcified matrix. A thin layer of osteoid tissue lies between the single epithelioid layer of osteoblasts and the bone. An osteoclast in the lower left portion of the picture has begun to separate a spicule of bone. A very young marrow space is near the center.

FIG. 11.—A small piece of cartilage has been completely replaced by bone and bone marrow at the end of three weeks. The bladder epithelium surrounds the region and in one place occurs as a papillary prolongation. The periosteal layer can be distinctly seen next to the bone, particularly in the upper portion.

distributed up to the area adjacent to the line of ossification. Although here the cells are moderately compressed, the lacunae and their cells retain their identity and appear quite distinct. In this same region the character of the intercellular substance changes so that the collagenous fibers of the cartilage are visible. These fibers and the rest of the matrix become more confluent and stain more deeply. The calcified zone changes almost abruptly into an ossified zone, however, without a strict line of demarcation. Most of the lacunae disappear. A few of the cells are enmeshed apparently in the newly formed bone which is being laid down on the calcified cartilage by a single row of osteoblasts that line the peripheral margin of the bone (Fig. 10).

Several spicules of bone have been made and displaced from the zone of ossification by this method. The spicules are separated as they are ossified presumably by two methods. Osteogenic tissue is found enclosed in small

spaces which increase in size particularly lengthwise, separating the spicules from the zone of ossification as the process is completed. The osteogenic tissue or primitive marrow multiplies and provides among other things osteoblasts for the deposition of new layers of bone on the spicules that have separated. Simultaneously the separation of spicules is aided by the resorption of bone by a few osteoclasts found lying in little depressions which they have hollowed out in the new bone. The peripheral bone spicules that have been separated are partially surrounded by a layer of osteoblasts and are separated from the adjacent bladder cells by a small amount of loose connective tissue. Between the bone spicules are comparatively large spaces filled with bone marrow. In the meshes of the reticular connective tissue are found a profusion of the many different types of marrow cells. This process of bone formation is rapid. At the end of 21 days small areas of cartilage have been

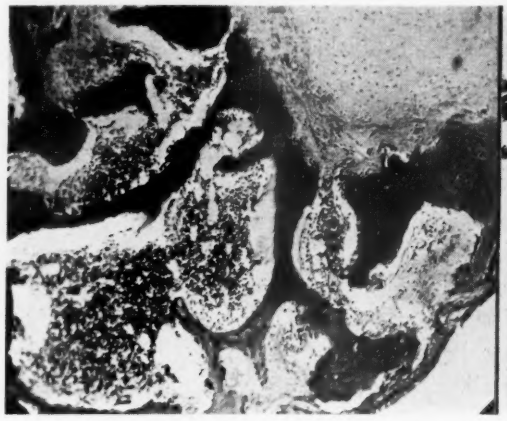

FIG. 12.—Cartilage is being replaced directly by bone. This process at the end of eight weeks is essentially the same as the one found at the end of three weeks and is shown in Figs. 9 and 10.

FIG. 13.—A thin layer of bladder epithelium surrounds the bone which had its inception in perichondrium. The layer of very active osteoblasts can be seen adadjacent to a thin layer of osteoid tissue which is beside the bone.

completely replaced by spongy bone and marrow. The spicules tend to anastomose to form trabeculae and are surrounded in part by periosteum (Fig. 11).

This process of bone formation is found in sections made from older experiments. The region of the collagenous fibers between the normal cartilaginous matrix and the bone is wider and is more vascular than is found earlier. The bone is sharply demarcated from this latter region (Fig. 12).

The perichondrium about the cartilage at a distance from the bladder epithelium has little evidence of activity. However, in a region where the epithelium is adjacent to perichondrium and cartilage there is evidence of marked activity. The cells of the cartilage proliferate and the matrix becomes calcified. Osteoblasts are formed from the perichondrium and from osteogenic tissue between the cartilage and the wall of the cyst. These osteoblasts rapidly produce layers of bone which replace the cartilage. Moreover, bone

is readily formed where bladder epithelium and perichondrium only are adjacent to each other (Fig. 13). The cells of the inner layer of the perichondrium multiply rapidly and osteoblasts are formed that promptly manufacture bone. In this region may be seen very well a thin layer of material immediately adjacent to the row of osteoblasts that stains pink rather than red with eosin. As this so called osteoid tissue becomes ossified a few of the osteoblasts are enclosed in the bone and so become osteocytes. As the deposition of bone continues the character of the cells of the inner layer of the perichondrium changes. The nuclei become more numerous, mitosis is common, and the cells do not stain so deeply with eosin. This layer of tissue may now be referred to as periosteum. The outer side of the spicule of bone is very close to the cyst wall, only a thin layer of cells intervening, some of which are osteoblasts. It appears though that the lamella are nearly all laid down on the periosteal side. Small marrow spaces may be seen in the young bone.

Bone may be formed directly from connective tissue under the influence of growing bladder cells, in addition to the different methods of replacing cartilage by bone that have been described. This former process is similar to that which was first noted by Huggins.[1] Sections made from short term experiments show a spicule of bone to have already formed (Fig. 14). It is apparently separating from a sharply demarcated zone of calcified connective tissue derived from abutting connective tissue. The sharpness of the change from uncalcified to calcified connective tissue and to bone without visible agents between the layers of tissue is notable. On the edge of the bone peripheral to the site of ossification is a layer of osteoblasts. These cells also surround the bone near the cyst wall. Small round areas of primitive marrow can be seen in the spicule of bone and in larger areas adjacent to it.

A few of the sections made from older specimens indicates that under the influence of the epithelial cells of the cyst wall, cartilage may be formed from dense connective tissue which in turn is replaced by bone (Fig. 15). In portions of the zone of calcified tissue may be seen lacunae. This region of cartilage is invaded by osteogenic tissue which leaves septae and islands of calcified tissue that are surrounded by osteoblasts and osteogenic tissue. The osteoblasts lay down new bone about the remnants of cartilage and in connective tissue. Ossification proceeds in this manner until bone formation is complete.

RÉSUMÉ AND COMMENTS

Small defects in hyaline cartilage of the dog failed to regenerate in six months after costal chondrectomy even though the perichondrium is not removed. The experimental defects in the cartilage become filled with fibrous tissue. Similar defects in costal cartilage that have been bridged by autogenous transplants of urinary bladder mucosa become filled after a time with a mass consisting of spongy bone, bone marrow, and epithelial cysts. Under the influence of the proliferating cells from the transplanted bladder mucosa,

FIG. 14.—The bladder epithelium can be seen surrounding a spicule of bone that has been formed alongside a layer of densely calcified fibrous tissue.

FIG. 15.—In this specimen the fibrous tissue was changed into cartilage and then into bone by some influence of the bladder epithelium that is seen growing in the lower part of the picture.

the cartilage cells hypertrophy and create greatly enlarged lacunae. The calcified matrix is broken into particles which become ossified by the invasion of newly formed blood vessels and young connective tissue, in which osteoblasts and primitive marrow cells are constantly differentiating. The histologic picture closely resembles endochondral ossification that takes place in the calcification zone of the epiphyseal ends of the growing long bones where hyaline cartilage is replaced with osseous tissue. Bone resorption and replacement, however, do not follow the original bone formation in our experiments, nor does the costal cartilage constantly proliferate to furnish new material for invasion by osteogenic tissue as ordinarily happens at the ossification center of an epiphysis. Simultaneously with the preceding process there may be formed a layer of perichondral bone from the inner layer of the perichondrium. The perichondrium becomes periosteum with the deposit of perichondral bone. None of the sections reveal any evidence that perichondrium has been stimulated to produce cartilage.

The repair of experimental fractures apparently has many features that are analogous to the endochondral ossification that occurs under the stimulus of bladder epithelium. Ham[12] found the usual repair of a fracture in rabbits to be due to osteogenic cells capable of differentiating into either bone or cartilage. The matrix of the cartilage of the callus becomes calcified, the lacunae enlarged and coalesced. This region is invaded by osteogenic cells and the calcified matrix differentiates directly into bone.

A less common but a more direct replacement of cartilage by bone is accomplished under the influence of the proliferating bladder mucosa. Osteoblasts deposit a layer of osteoid tissue, which quickly become bone, upon a zone of heavily calcified matrix. The transformation from cartilage to bone is speedily accomplished without the destructive changes in the cartilage that we have described as simulating the calcification zone of an epiphysial end of a long bone. Apparently the calcified matrix acts as a local deposit of calcium salts for the adjacent osteogenic tissue which has given rise to osteoblasts and marrow. This process is not strictly analogous to direct or intramembranous ossification in that this latter method characteristically is not associated with cartilage but is formed directly from embryonal connective tissue. The replacement of cartilage by bone is direct, however, and as in intramembranous bone formation the bone is formed through the medium of osteoblasts. The osteoblasts, in part at least, seem to deposit their hyaline ground substance upon collagenous fibers of the disintegrating calcified cartilage. The growing bone trabeculae may be surrounded by periosteum and the spaces between the spicules are abundantly filled with marrow. The production of hematopoietic marrow in all of the experiments is as striking as the bone production.

The latter method of production of bone from calcified cartilage is almost identical with the production of bone from calcified dense connective tissue. It is not surprising that in some instances that fibrous tissue should be changed into cartilage in the process of ossification. The change is quickly made and seemingly is accomplished under the influence of bladder epithelium.

The histogenesis of the bone is the same in the different types of ossification found in our experiments in that the bone is actually formed by osteoblasts. Osteoblasts are formed readily from young connective tissue under the influence of bladder epithelium.

The nature of the agent derived from proliferating mucosal cells of a urinary bladder transplant or their products is not known but is presumably a physiochemical one. It has been shown to induce bone formation in certain connective tissues, to stimulate osteogenesis in experimental bone defects, to produce endochondral and a more direct type of ossification, to stimulate bone formation from perichondrium and periosteum, and to give rise to capillaries and large amounts of marrow. By inference the same force or a similar one is present at the ossification center of an epiphysis or at the site of a fracture. The agent is in effect a stimulus to growth and it gives rise to speculation whether it might be a ferment-like substance needed directly or indirectly in some fundamental way with the process of growth. Possibly it is produced normally by the urinary bladder analogous to the growth hormone of the anterior pituitary.

The observations of Leo Loeb[13, 14] in 1906 are of interest when considering the stimulus that epithelial cells may apply to connective tissue. He noted the appearance of a spindle cell sarcoma in the course of the transplantation of a carcinoma into a Japanese mouse. The epithelium apparently transmitted its stimulus to grow to connective tissue of either the original animal or of the host. As a result of the stimulus emanating from the carcinoma the connective tissue assumed a sarcomatous growth. Sections of the mouse tumor showed spindle cell sarcomata beside carcinomatous tumors.

The derivation and nature of the osteogenic tissue that forms under the influence of bladder cells and gives rise to the changes that have been described in the cartilage and perichondrium are not finally determined by our experiments. The experiments do suggest the nonspecificity of certain connective tissues which as a result of a stimulus may acquire osteogenic properties and are capable of differentiating into cartilage, bone and marrow, capillaries, osteoblasts, osteoclasts and multinucleated cells. The evidence is convincing that adult bone cells are not necessary for the development of new bone. The perichondrium which appears histologically to be similar to periosteum may respond functionally by giving rise to either cartilage, bone, or periosteum. The young connective tissue cells adjacent to the proliferating bladder epithelium and the ones that first come under their spell seem to substantiate an opinion of Maximow. He believed that connective tissue contains numerous undifferentiated mesenchymal cells, especially arranged along capillaries, capable of producing any type of connective tissue or blood cell. Our experiments do not indicate that the young connective tissues, or fibroblasts revert to an earlier type of cell (anaplasia) but rather that multipotent cells are stimulated to further differentiation into capillaries, osteoblasts, multinucleated cells, etc., by the bladder epithelium. It does not seem likely to us that the changes that have been described in our experiments are a result of

the local stimulation by bladder mucosal cells of specific undifferentiated osteogenic cells which have a widespread distribution in the body and have an inherent tendency to form bone alone.

CONCLUSION

Further experimental evidence is presented that the proliferating cells from an autogenous transplant of bladder mucosa of the dog give rise to an agent, which directly or indirectly, has the potentiality of altering the function of certain adult connective tissue.

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THE CLINICAL SIGNIFICANCE OF EXPERIMENTAL STUDIES IN WOUND HEALING*

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IT IS commonly stated that the results of experimentation upon the animals commonly employed in the laboratory are not capable of transfer to man and therefore that such studies are of little importance. Usually this argument is based upon the obvious fact that not only does man differ to a great degree from even other primates, but also upon a second equally obvious fact that it is impossible to duplicate in the laboratory the exact conditions obtaining in the clinic. So, in wound healing, one says the characteristics of the phenomenon in the rat have no bearing upon what may happen in man, for they are widely differentiated species, and, following a wound, the rat does not cough, vomit, or undergo many of the vicissitudes to which man is liable.

The argument, it seems to us, overlooks the primary purpose of the experimental method, whether concerning problems in biology or in the more limited field of that subject having to do with man. It is not an attempt to duplicate in the laboratory animal phenomena as seen in the clinic—this of course is impossible—but rather to simplify the situation by reduction of the variables to the point where generalizations may be deduced from controlled observations, and which may then be tested as to their validity by observations made on man. When such generalizations are found to be true, it is then possible to interpret and to predict phenomena which would otherwise be misunderstood or unforeseen. It is with this viewpoint that we wish to consider some of the results that have been obtained in the experimental study of wound healing in our laboratories.

The attempt has been made to simplify the problem by observing one function of the healing wound which is readily measurable, namely, the tensile strength. This when considered in terms of time enables one to observe with approximate exactitude the different phases of healing, and by introducing controllable variables to determine their effect.

It became apparent at once that the curve of the velocity of the healing wound resembles that of growth in general, which in turn is like that of the growth of a population. Therefore the deduction was made in correlation with the histologic picture that we are dealing primarily and essentially, so far as the function of tensile strength is concerned, with the growth and maturation of the fibroblast. From this study, one is able to say that fibroplasia starts abruptly at the fourth day and proceeds with decreasing velocity

* The expenses of the experimental work upon which this paper is based were defrayed by Davis & Geck, Inc.

until a maximal strength for this phase of healing is reached around the twelfth to the fourteenth day and that by the sixth, approximately one third and by the eighth, approximately two thirds of this strength is obtained. This, of course, is readily checked against and correlates with surgical experience. This phase of fibroplasia has been studied in wounds of all tissues in which the normal tensile strength is greater than the maximum of the fibroplastic process and the velocity curves of fibroplasia are identical in type. A second generalization may be made to the effect that the healing of a wound in so far as the phase of fibroplasia is concerned is a phenomenon common to all tissues, irrespective of the specific differentiation primarily involved. This, while not so apparent, correlates also with surgical experience in man.

This same phenomenon, that is, fibroplasia as measured by the tensile strength, has been studied in the same tissues in several species of animals and again there appears the common lag period, and a similar growth curve reaching a maximum in the same time. This suggests that one is dealing with a basic phenomenon common not only to all tissues but to all animals tested, and leads one to question the commonly accepted view that the fibroblast involved in the healing of a wound is derived by differentiation from the already differentiated fibroblasts of the fixed tissues involved. On the contrary, the generalization is proposed that the fibroblastic phase of the healing of a wound is initiated by and derived from wandering and residual mesenchymal elements, very slightly, if at all, undifferentiated from the embryonic mesenchyme, and which are present in all tissues. This abstraction unfortunately is not susceptible of correlation in man or for the moment of direct experimental test, although much supportive evidence may be found in the studies of histogenesis of these cells both in vivo and in vitro. At least it provides a concept which is in substance that the fibroblastic phase is a characteristic basic phenomenon in itself, derived from resting undifferentiated tissue and resulting at its close in relatively undifferentiated fibrous tissue, which in its most obvious form is the scar.

We want to make the point clear, if we can, that the concept we have is not that the primary healing of a wound is due to cells derived from adjacent fixed tissues, but from cells which appear in the early exudative process, and which, by growth or differentiation, become fibrous cells, and that the scar tissue itself is not a differentiated connective tissue, but is the result of a process specific in itself.

Having thus established a normal curve for this phase of the healing of a wound, it is of importance to know what may either accelerate or decrease the velocity of the process. There are theoretically two changes that may occur; the one, the initiation of the process may be quickened or delayed, the other, the growth and maturation of the fibroblasts may be either hastened or retarded. By no means have all the possible factors which may affect this process been tested. Certain fundamental variables have been studied, however. It has been found that the initiation of growth occurs somewhat earlier in the young, but that once started it proceeds at the same rate, and that a

high protein diet accelerates to a certain degree the velocity of growth, perhaps as a result of the so called "dynamic action" of protein. This, of course, suggests that an increased metabolism may have a similar effect. Otherwise, the general and systemic factors seem to have but little or no action, unless they are so severe as to derange the chemical balance of the subject to a degree that in itself threatens its survival. This is the case in man, in the debilitated and dehydrated infant or elderly person, and in the experimental animal where conditions probably produce a delay in the initiation of fibroplasia.

A similar delay occurs as a result of any local situation which increases the exudative reaction in the wound. Infection, trauma, mechanical or chemical, the presence of dead tissue such as blood clot or suture material, act for the most part by retarding the onset of fibroplasia, rather than by inhibiting the growth of fibroblasts once initiated. These observations bring no new knowledge to the clinic but should serve to emphasize once again the necessity for the protection of tissues from damage, mechanical or chemical, for the obtaining of as perfect a hemostasis as possible and for the burying of only that quantity and kind of suture material which is essential in assuring the continuity of the wound until it attains the necessary strength. One must constantly keep in mind that the process of healing, although easily retarded, is expedited with difficulty, and that retardation is the result of anything that will intensify or prolong the exudative phase of wound healing.

We want to emphasize that the suture material customarily used by the majority of men, namely, catgut, is not only a foreign body, but a foreign body which induces exudative reaction, and, therefore, delays the initiation of fibroplasia. This is theoretical when the amount of catgut used is small. It is not theoretical if the amount of catgut placed in the wound is great. Under such circumstances, without any infection whatsoever, there will be delay in the initiation of fibroplasia and, therefore, delay in the healing of the wound.

Silk does not induce an exudative reaction and in the fine sizes that should be used is an innocuous substance. On the other hand, one has to face the fact that even in the best of our hospitals the amount of infection that occurs is appreciable and therefore it is probably good sense in most institutions to use a suture material which disappears in the presence of infection.

Fibroplasia, having produced an undifferentiated tissue as a result of the proliferation of mesenchymal elements of low differentiation in themselves, one wishes to know what further may happen to the wound. It is obvious that certain structures heal eventually with restoration of function, as do bone, tendon and fascia. In others the scar serves to preserve the continuity of an organ, such as liver, kidney, stomach and intestine, and skin. In general, however, where the function is a mechanical one, differentiation of the fibroblasts resulting from the first phase occurs to meet the functional necessity. The most striking example is in the healing of fractures with the change from fibroblastic to osteoid tissue and from this to true bone. On the

other hand, where such highly differentiated fibrous tissue is not primarily involved in the wound, then the differentiation of the fibroblast is much less marked. As a generalization one may say that the differentiation of the fibroblast involved in the first phase of healing of the wound, proceeds in the same manner and to the same result as it does in the growth and differentiation of the embryo. In the embryo the bone, for instance, is differentiated from the mesenchyme by factors we do not know with any accuracy. I doubt if we know with any accuracy what induces the differentiation of a scar as in a fracture, but in all probability it is the same factors that are involved. Therefore it may be deduced that the differentiation of simple fibroblastic tissue into highly organized connective tissue structures is governed by the same factors that control the process in the embryo to which embryologists are devoting much attention at the present time. Correlative of this is experimental evidence which we have obtained, incomplete but suggestive, that such differentiation varies according to species and directly as the rate of embryologic differentiation, or, in other words, as the rate of growth of the species concerned.

The factors other than this that may affect the rate of differentiation have been only partially studied, but again as in the first phase only the extremes of variations in diet seem to have any influence upon the differentiation of bone. The second phase of differentiation, like the first of fibroplasia, is a fundamental thing closely allied to the similar process in the embryo.

SUMMARY

From experimentation, generalizations may be derived which may receive correlative support in the clinic. Such experimental investigation of wound healing leads to certain generalizations as follows:

(1) The healing of a wound is a variant of growth, and a fundamental biologic phenomenon.

(2) The healing of a wound occurs in two phases, the first, that in which the most characteristic phenomenon is fibroplasia, and the second, that in which the fibroblasts so produced are differentiated into specific adult tissue.

(3) The first phase, that of fibroplasia, originates in and from resting, relatively undifferentiated cells closely related to the mesoblast.

(4) The second phase, that of differentiation, occurs as a result of and in the same manner as the original differentiation of these structures from the mesoblast.

(5) The healing of a wound is disturbed only by profound systemic changes, but locally healing is readily delayed by a retardation of the phase of fibroplasia as a result of an excessive exudative reaction.

(6) These generalizations are true of the common animals used for experimentation in the laboratory, including the primates, and also of man.

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DISCUSSION.—DR. DALLAS B. PHEMISTER (Chicago, Ill.).—The different varieties of connective tissue are repaired by cells derived largely from those tissues. While the early stage of repair is morphologically similar in each and may be grouped together under the heading of fibroplasia the later stages for each are different. This means that the cells active in the fibroplasia have potentialities for further differentiation according to the tissue from which they spring. Thus, newly laid down fibrous tissue from injured bone has a greater tendency to undergo metaplasia into bone than a morphologically similar tissue derived from injured fascia. Also there is not the same tendency to metamorphosis into the maturer tissue in all species. Thus, in the dog, bony union follows in all cases of fracture without loss of substance whereas non-union is fairly common in fractures in man.

DR. EDWARD L. HOWES (New Haven, Conn.).—I would like to emphasize one or two points briefly mentioned by Doctor Harvey, and especially to indicate the phase of wound healing which really can be influenced by surgical skill. Of the periods of healing which we have demonstrated, only the time when the wound depends on the sutures for strength can be affected. Tissue necrosis or infection or foreign bodies prolong its duration and delay the onset of fibroplasia. However, once generation of fibrous tissue is initiated the process of fibroplasia proceeds at a uniform rate as a general rule, despite the difficulties which delayed its onset. The infected wound remains weak, therefore, not because the rate of fibroplasia is lessened, but because the onset of the fibrous generation is delayed. This failure of fibrous tissue generation may occur only in a small portion of the infected wound, or along the entire length of the incision. In healing per primam, on the other hand, the generation of fibrous tissue nearly always begins throughout the wound at about the same time and in the shortest length of time after the injury. We as surgeons, then, have under our direct control the time when the wound will begin to gather strength—and this is the important point—that by careful surgical technic, with the minimizing of infection and contamination in the wound, and with the insertion of small amounts of suture material, we force the generation of the fibrous scar to begin in the shortest length of time after the wound is made.

The maximum strength attained by the linear scar after the period of fibroplasia depends on the thickness of that scar, for its entire mass consists solely of undifferentiated connective tissue. The strength of the scar is, moreover, in proportion to the original strength of the tissue wounded as the density and differentiation of the regenerated fibrous tissue is to the proportion and differentiation of fibrous tissue in the original tissue wounded. It follows accordingly that if the tissue is cut in such a way that its greatest strength is interfered with, as, for example, if the differentiated bundles

of fascia are cut across, a greater strength has to be regenerated ultimately by the scar through the process of differentiation than if the bundles were merely separated. Thus less strength has to be generated by healing of the wound in muscle than in fascia, for the density of fibrous tissue in the original structure is less than that in the scar. Clinical experience has for some time furnished one striking example of these facts which we can now recognize as a general principle. The McBurney incision simply divides the muscles and because the function strength of the tissues has sustained the least amount of interference the healing wound replaces this strength lost in a shorter length of time than if the muscles had been cut across with loss of all function.

Dr. John J. Morton (Rochester, N. Y.).—I should like to add that Doctor Harvey has not brought out here the correlation between the size of the suture material and tissues involved in healing. I think, from a practical surgical standpoint, that this is one of the most important things which he has shown. I wish he had mentioned it in his present consideration.

Doctor Graham.—I would like to ask Doctor Harvey what effect general anemia and intoxication, as, for example, by prolonged general anesthesia, has on these curves.

Dr. Samuel C. Harvey (New Haven, Conn.).—We have not tried out the effect of anemia nor experimented with the results of prolonged anesthesia. Of course one should not prophesy, but in general, in our experiments, we have been unable to find any systemic things which have any effect on this fundamental process of healing, aside from the age factor and possibly the high protein intake, which is probably, I think, related to a metabolic influence.

Replying to Doctor Morton relative to the size of catgut to tissues sutured, I have referred to this so often I hesitate to do it again. The practical thing, of course, is that there is no point at all in introducing a suture into the tissue which has greater strength than the tissue itself. That is, to use a suture of zero plain catgut in approximating fat is quite ridiculous because the fat itself has no holding power. The finest possible suture is more than sufficient to approximate fat. When it comes to approximating fascia, which is the thing we depend upon in the main, there again we have, I think, an exaggerated idea of the holding power of fascia in respect to the size of suture.

If any of you will try the simple test in your next laparotomy, of taking a double zero chromic catgut suture or one of fine silk, passing it through the edge of the fascia with a good bite and then yanking upon the suture, you will find the suture comes out of the fascia and does not break unless you have extraordinarily poor suture material. In other words, there is very little point in putting, as many do, No. 1 and 2 chromic catgut in fascia, for it is about ten times stronger than the holding strength of the fascia itself.

The reason for not using large suture is, as I have emphasized previously, that the less foreign material you put in, and catgut is definitely foreign material because it is absorbed by an exudative reaction which delays the onset of hyperplasia, the better will be the healing of the wound. Of course, this all goes back to the original contention of Doctor Halsted, for, not only the delicate handling of tissues and perfect hemostasis but also for the use of very fine suture material of a harmless nature.

A STUDY OF DEHYDRATION IN HUMANS

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IN THE course of our investigations on the water exchange of surgical patients it became apparent that a knowledge of the quantity of fluid the body loses in order to become seriously dehydrated is important. From previous studies we are able to calculate the amount of water needed by any given patient to maintain a satisfactory water balance. Some patients, however, are admitted to the surgical wards in a seriously dehydrated condition. For them, the immediate need is for more than a maintenance supply of water. A calculation of their water requirements must include an amount of water for the return of body fluids to the normal level. If it were known how much fluid is lost to produce serious effects, an allowance could be made for the water to hydrate these patients in a fairly accurate quantitative manner. A study is presented that furnished data on this problem.

It was first necesary to define some measure of serious dehydration. Clinical observations, such as the degree of dryness of the skin or tongue are factors which are difficult to grade. For our purpose it was decided that a lack of water for the normal excretion of waste materials by the kidneys was an important serious effect of dehydration and a particularly suitable one to use as an index of dehydration, since its presence would be shown in a somewhat quantitative manner by a rise in the nonprotein nitrogen of the blood to abnormal values. On this basis, the water exchange of two healthy adult male subjects was followed over a period of several days' time during part of which dehydration was produced by withholding water until the nonprotein nitrogen of the blood increased to above 40 mg. per 100 cc. There is also presented a study of the water exchange of a patient from the time of her admission to the hospital in a condition of dehydration comparable to that produced in the experimental subjects up to the time of restoration of her body fluids. This permitted a comparison of the data from the experimental subjects with that of a clinical case.

EXPERIMENTAL SUBJECTS: *Procedure.*—During the entire period of the study, the two subjects, J. N., age 26 years and R. M., age 63 years, followed a constant routine of light activity, which consisted mainly of walking to and from the hospital and a definite distance outdoors each day. Their only restriction was that they avoid sweating and keep themselves just comfortably warm by adjusting the amount of their clothing. The water exchange of these two subjects was determined by the method of Newburgh and his associates.[1] The weighing of the subjects was done on a special scale accurate to 1 Gm. The weight of all ingesta and excreta was obtained on a small

scale accurate to 0.5 Gm. An important part of the method was the calculation of the caloric expenditure of a subject from a determination of the insensible loss of weight and the urinary nitrogen. On the basis of this calculation during the first part of the preliminary period, a maintenance diet was made up for each subject and given during the remainder of the study. The foods selected were of a low water content. The mineral content of the diet was essentially constant, so that after a short period the amount of salts and end-products of metabolism offered to the kidneys for excretion was the same each day.

The preliminary period was continued until the subjects showed a fairly

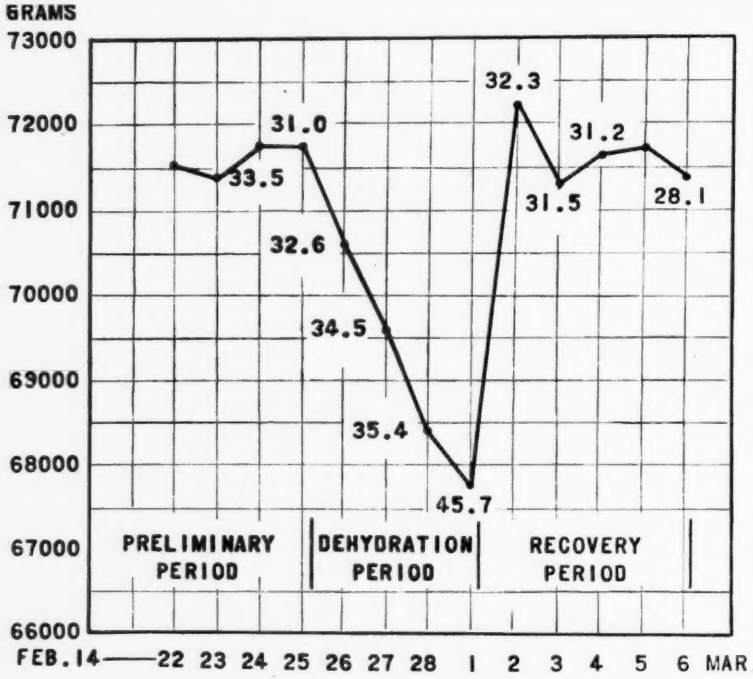

FIG. 1.—Daily weight of subject J N., with figures along the curve indicating the blood nonprotein nitrogen in mg. per 100 cc.

constant weight. The dehydration period was then started by withholding water. The progress of the dehydration was followed by a determination of the nonprotein nitrogen of the blood at the end of each 24 hour period, which ran from 8 A.M. to 8 A.M. When this value had increased to above 40 mg. per 100 cc. the dehydration period was terminated and water was given *ad libitum*.

During the course of the study, estimations of the concentration of the venous blood by means of an erythrocyte count, a hematocrit reading (0.8 to 1.0 cc. of oxalated blood in 1 cc. graduated centrifuge tubes), and a specific gravity determination (2 cc. Gay-Lussac specific gravity bottle) were made at the same time each day. The McClure-Aldrich intradermal salt solution test [2, 3] was also carried out on each subject daily. The result of this test in

relation to the dehydration will be reported later. The mouth temperature was determined by means of a standard Fahrenheit clinical thermometer. The effect of the dehydration on kidney function was also studied. The specific gravity of the urine was obtained by means of a specific gravity balance.

RESULTS: *Changes in Weight of Subjects.*—It is obvious that if an individual is fed exactly what he metabolizes, any change in his weight from day to day must be due to a retention or a loss of water. Since this was approximately the condition for the experimental subjects, the progress of the dehydration and recovery from it could be followed by noting the changes in their weight. This is shown graphically for subject J.N. in Fig. 1. The

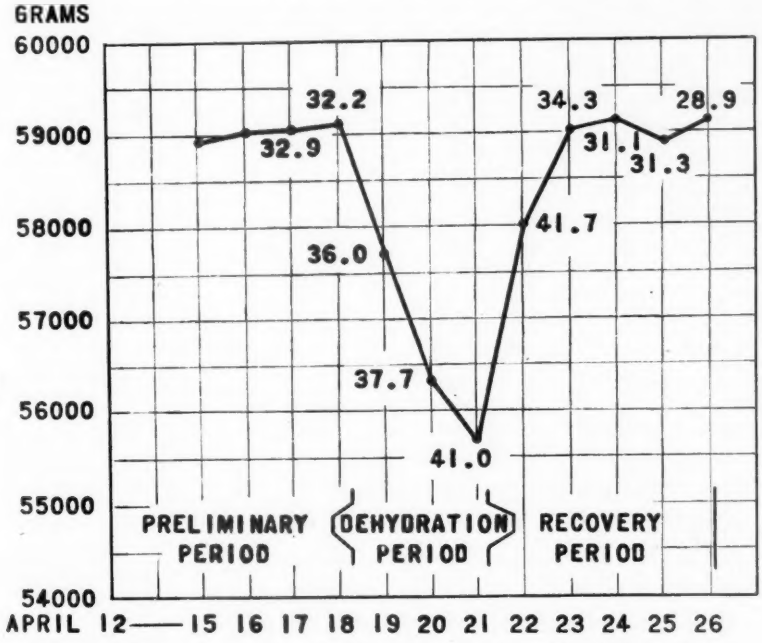

FIG. 2.—The same data for subject R.M. as shown for subject J.N. in Fig. 1.

figures along the weight curve indicate the daily nonprotein nitrogen in mg. per 100 cc. of blood. This subject lost about 4 Kg. of weight during the four days of his dehydration. On the first day of the recovery period an intake of a little more than six liters of water returned his weight to slightly above that of the preliminary period. The same data for the older subject, R.M., age 63, are shown in Fig. 2. He lost nearly 3.5 Kg. of weight when water was withheld for three days. At the end of this period he was just as thirsty as the younger subject, but was afraid that too much water would make him sick. With a comparatively moderate fluid intake, two days were required to bring his weight up to the previous level.

WATER BALANCE OF SUBJECT J.N.

The water exchange of subject J.N. is summarized in Table I.

Preliminary Period—12 Days.—The water exchange of only the last two days of this period are shown in Table I. The water drunk is an average amount for many individuals. The water content of the food is low, since it was selected for its dryness.* The water of oxidation and preformed water are endogenous sources of available water in contrast to the water drunk and the water content of the food being exogenous forms. The water of oxidation is formed on the combustion of protein, fat and carbohydrates. The total amount of water thus made available depends upon the amounts of these substances oxidized. In this instance the process furnished nearly a pint of water a day. Preformed water is the term applied in water balance to the water content of the individual's own body tissues. When body tissues are broken down and oxidized for food, as in starvation, the water content of that tissue becomes available for general purposes. Conversely, in overnutrition body tissue is formed and water is taken from the general supply to make up the water content of this new tissue. Preformed water then can be a

TABLE I

Water balance of subject J.N.

DATE, 1935	FEB.24	FEB.25	FEB.26	FEB.27	FEB.28	MAR.1	MAR.2	MAR.3	MAR.4
WEIGHT IN GRAMS OF:	PRELIMINARY PERIOD		DEHYDRATION PERIOD				RECOVERY PERIOD		
WATER DRUNK	2095	1841	0	0	0	514	6151	1698	2517
WATER CONTENT OF FOOD	261	263	296	288	259	262	273	288	288
WATER OF OXIDATION	424	435	418	367	409	406	510	481	485
PREFORMED WATER	0	-13	-26	-30	-27	-27	-17	+32	+37
WATER OF URINE	1031	1102	472	481	442	446	742	1586	1339
SP.GR. OF URINE	1.016	1.016	1.031	1.032	1.037	1.038	1.024	1.016	1.021
WATER OF STOOL	17	38	43	40	86	2	0	97	22
BLOOD	10	11	13	15	22	48	24	24	8
N.P.N. IN MG. PER 100 C.C.	33.5	31.0	32.6	34.5	35.4	45.7	32.3	31.5	31.2
WATER VAPORIZED	1348	1385	1325	1149	1295	1283	1638	1549	1562
MAX. MOUTH TEMP. °F.	98.4	98.8	98.8	98.7	99.0	99.4	98.3	98.7	98.4
TOTAL AVAILABLE WATER	2780	2526	688	625	641	1155	6917	2499	3327
TOTAL WATER OUTPUT	2406	2536	1853	1685	1845	1779	2404	3256	2931
WATER BALANCE	+374	-10	-1165	-1060	-1204	-624	+4513	-757	+396

AMOUNT OF FLUID LOST IN DEHYDRATION PERIOD: 4053 GRAMS
IN RELATION TO TOTAL BODY WEIGHT OF SUBJECT 71500 GRAMS = 5.7 PER CENT.

positive or negative factor in water balance. Since the diet was approximately that of the subject's metabolic needs, there was little undernutrition or overnutrition to deal with and preformed water was of an insignificant amount.

The water of the urine during the preliminary period was of a moderate amount and the blood nonprotein nitrogen was well within the limits of normal. The water lost in the stools was of the usual insignificant quantity when compared with the excretion of water through other channels. The blood losses shown represent amounts withdrawn for chemical studies.

The insensible vaporization of water from the skin and lungs is commonly neglected in estimations of water output. The importance of recognizing this channel of water loss is brought out by the fact that during each day of the study, excepting March 3, the output of water by vaporization from the skin and lungs was greater than the output of water in the urine. In a previous article on the water balance of surgical patients[4] we showed that for the simple uncomplicated case this water loss varied from 1000 to 1500

* Diet of J.N. in Gm.: Bread—210, butter—70, cornflakes—40, cream 40 per cent—230, sugar—35, jelly—50, lean round beef—150, unsalted potato chips—40, mints—75, English walnut meats—30.

Gm. per day. With fever, hyperthyroidism, or the sweating of hot and humid environments, the water vaporized generally amounted to from 1500 to 3000 Gm. per day, with an average of almost two liters per day. The figures given for J.N. during the whole period of study are a fair average for a healthy young adult weighing approximately 71.5 Kg. and carrying on a general routine of light activities.

Water balance values of 374 Gm. of hydration on February 24 and a dehydration of 10 Gm. on February 25 are examples of the small variations that occur in any individual's weight from day to day.

Dehydration Period.—No water was drunk by J.N. during the first three days of the dehydration period. On the fourth day, March 1, he was unable to eat his food because of insufficient saliva, so about two-thirds of a glassful of water had to be given with each meal, the total being 514 Gm. of water for the day. As soon as the intake of water was limited the output of water as urine diminished to about 450 Gm. per day. As the dehydration progressed the specific gravity of the urine increased, showing that waste materials were being excreted in greater concentrations. In spite of this effort of the kidneys, the retention of nitrogenous material in four days was sufficient to raise the nonprotein nitrogen of the blood from the average of 32.3 for February 24 and February 25 to the above normal value of 45.7 mg. per 100 cc. At this time J.N. showed all the clinical signs of a serious dehydration. His eyes were sunken; his skin was dry and hot; his tongue was completely dry and leathery, and a slight degree of fever had been present for the previous 48 hours. The occurrence of these objective findings justified our use of an elevated blood nonprotein nitrogen as an index of a serious depletion of body water. It would have been beyond the realm of experimental work to have carried the dehydration further. The total fluid loss of 4053 Gm. during this period will be discussed later.

TABLE II

The effect of dehydration on the concentration of the blood of subject J.N.

DATE. 1935	WATER BALANCE GM.	ERYTHROCYTES PER CU. MM.	HEMATOCRIT PER CENT	SPECIFIC GRAVITY
PRELIMINARY PERIOD				
FEB. 23	-150	5610000	49.50	1.0598
24	+374	5110000	47.96	1.0575
25	+10	5170000	48.50	1.0598
DEHYDRATION PERIOD				
FEB. 26	-1165	5370000	48.81	1.0601
27	-1060	5390000	50.14	1.0623
28	-1204	5860000	50.81	1.0631
MAR. 1	-624	6060000	50.62	1.0652
RECOVERY PERIOD				
MAR. 2	+4513	5770000	49.31	1.0604
3	-757	5210000	47.18	1.0603
4	+396	5380000	48.91	1.0619

Recovery Period.—On the first day of the recovery period, J.N. was told that he could have all the water he wanted, with an admonition to drink small amounts at first. On this first day he took in 6151 Gm. of water and began to feel much better. The distribution of this first water was of particular interest. As shown by the positive water balance of 4513 Gm. and the return of the subject's weight to slightly above the normal

level (Fig. 1), approximately two thirds of it was retained by the body to replace water previously lost. This water was not merely left for the tissues after the other water using processes had been cared for, but the tissues were given preference in their demands for water even at the expense of water for kidney function. This point is better shown in the water balance of subject R.M. and the patient B.L. and will be emphasized in commenting on their data. The urine water increase to 742 Gm. was sufficient to reduce the nonprotein nitrogen of the blood to the normal level.

On the second and third day of the recovery period, the ingestion of water was about that of the preliminary period. With no water depletion to deal with on these two days and the only preferred output of water being by vaporization from the skin and lungs, a fair amount of the total available supply of water was left for the kidneys. The water of the urine consequently amounted to 1586 and 1339 Gm. of water respectively and was of a moderate specific gravity.

TABLE III

The effect of dehydration on the kidney function of subject J.N.

DATE. 1935	WATER OF URINE GM.	SP.GR. OF URINE	TOTAL SOLIDS OF URINE GM.	NITROGEN OF URINE GM.	PRESENCE IN URINE OF PROTEIN	CASTS	RBC.
PRELIMINARY PERIOD.							
FEB. 18	1274	1.015	40.8		0	0	0
19	1431	1.012	41.2 AV. 40.1				
20	1151	1.019	39.2				
21	1433	1.015					
22	1448	1.013		10.30			
23	1012	1.016		8.70 AV. 9.31			
24	1031	1.016	39.1	9.46	0	0	0
25	1102	1.016		8.80	0	0	0
DEHYDRATION PERIOD							
FEB. 26	472	1.031	31.8	6.32	0	0	0
27	481	1.032	36.6 RETENTION	7.00 RETENTION	0	0	0
28	442	1.037	38.0 9.9	8.08 5.20	SL.TR.	+	0
MAR. 1	446	1.038	44.1	10.64	TRACE	+	+
		1.041					
RECOVERY PERIOD.							
MAR. 2	742	1.024	48.1- EXCESS 8.0	14.48- EXCESS 5.17	SL.TR.		
3	1586	1.016	40.8	10.32	SL.TR.		
4					SL.TR.		
5					0	0	0

Blood Concentration During Dehydration.—In Table II are shown the data obtained from studies on the concentration of the venous blood of subject J.N. During the dehydration period the changes in the erythrocyte count, the hematocrit and the specific gravity furnished definite evidence of a diminished blood volume. With an adequate intake of water the data showed that the blood volume was rapidly restored to the previous level.

Kidney Function During Dehydration.—Significant data on the kidney function of J.N. during the important period of study are shown in Table III.

On the diet fed the total solids excreted in solution by the kidneys during the preliminary period averaged 40.1 Gm. per day. As a result of the insufficient supply of available water, on the first day of the dehydration period 31.8 Gm. of waste materials were excreted, giving a retention of 8.3 Gm. The amount of material to be excreted by the kidneys on the second day was the average of 40.1 Gm. from the diet, plus

the 8.3 Gm. of retention plus the salts set free when body water was lost as a result of the dehydration.* The conditions were thus becoming increasingly severe for the kidneys. With a greater concentration of urine, however, 36.6 Gm. of total solids were excreted on this second day. With the same vicious circumstances continuing, on the last day of the dehydration period the specific gravity of the 24 hour urine specimen was 1.038 and 44.1 Gm. of solids were excreted. A two-hour specimen of urine during this day showed a specific gravity of 1.041, which is the highest specific gravity observed by us for a urine specimen free of sugar and containing no more than a trace of protein. Ordinarily we consider kidneys to show normal function when they can concentrate urine to a maximum specific gravity of from 1.029 to 1.032.[5] The degree of dehydration produced, forced the kidneys of this healthy young man to an effort well above the normal maximum, but it was not accomplished without some evidence of kidney damage, J.N.'s urine on the last day of the dehydration period showing a trace of protein and more than the usual number of casts and erythrocytes. Even with a plentiful supply of water, four days were required before the proteinuria disappeared.

During the dehydration period the values for the total solids of the urine when compared to the average of the preliminary period showed a retention of 9.9 Gm. A similar calculation of the urinary nitrogen figures showed the retention to be 5.20 Gm., which accounts for more than half of the total solids retained, and which a more complete study of the effect of dehydration on kidney function by Dr. R. H. Freyberg of the Department of Internal Medicine[15] showed to be practically all urea nitrogen. A urine water output of 742 Gm. on the first day of the recovery period was sufficient for the excretion of the daily waste products and nearly all of the previous retention.

An interesting calculation can be used to show how the nitrogen retention of 5.20 Gm. during the dehydration period accounted for the increase in the nonprotein nitrogen of the blood from the average of 32.3 mg. per 100 cc. for the last two days of the recovery period to the abnormal value of 45.7 mg. per 100 cc. at the end of the dehydration period. This increase of 13.4 mg. per 100 cc. was not confined to the blood alone, but was spread equally through all body fluid. J.N. weighed approximately 71.5 Kg. Since he was somewhat dehydrated, his total fluid content amounted to approximately 60 per cent of his total body weight, or 42.9 Kg. If the 13.4 mg. per 100 cc. are multiplied by 42.9 the result is 5.75 Gm., a close agreement with the 5.20 Gm. of nitrogen retained.

WATER BALANCE OF SUBJECT R.M.

The conditions for the study of R.M. were slightly modified from those of J.N. The diet† was of a simpler arrangement and had sufficient fluids in it to enable R.M. to eat the food without water during the dehydration period. Then, in order to shorten the time for dehydration, which after the first day is rather an uncomfortable period, the subject maintained his customary activity, but spent part of the day and slept at night in a room kept at a temperature of 85° to 90° F. Slight sweating occurred and the water vaporized was greater in amount.

The water balance data of R.M. are shown in Table IV.

Preliminary Period.—7 Days.—With the exception of the low water content of the food and a blood loss, the water balance figures of April 17 and 18 are typical examples of normal water exchange.

* Since in this instance the dehydration was largely the result of the continuous insensible vaporization of water from the skin and lungs, the loss of body fluid substance with the water was negligible.

† Diet of R.M. in Gm: Cream 40 per cent—240, milk—200, unsalted crackers—60, butter—60, jelly—75, cheese—120.

Dehydration Period.—At the end of three days' abstinence from water, R.M.'s depletion of body fluids was sufficient to produce all the signs of serious dehydration, and his retention of urine wastes was great enough for the nonprotein nitrogen of the blood to have increased from 32.2 to 41.0 mg. per 100 cc. With a daily total available water of only 651 Gm., the water of the urine for this period was less than 400 Gm. a day. The specific gravity of this urine ran from 1.029 to 1.032, which is evidence of normal concentrating power of the kidneys.[5] The total of the negative water balance figures for the three days of dehydration amounted to 3397 Gm. This fact will be discussed later.

Recovery Period.—On the first day of the recovery period, R.M. was told that he could have all the water he wanted. He was afraid that too much water would make him sick, and as a result he only partially satisfied his thirst. The effect of this low water intake on the recovery from dehydration emphasized an important fact concerning water for the restoration of body fluids, the fact being shown as follows:

TABLE IV

Water balance of subject R.M.

DATE 1935	APR.17	APR.18	APR.19	APR.20	APR.21	APR.22	APR.23	APR.24	APR.25
WEIGHT IN GRAMS OF:	PRELIMINARY PERIOD		DEHYDRATION PERIOD			RECOVERY PERIOD			
WATER DRUNK	1457	1652	0	0	0	2392	2817	2558	1370
WATER CONTENT OF FOOD	362	362	363	363	363	359	359	365	363
WATER OF OXIDATION	304	310	310	310	310	310	310	310	310
PREFORMED WATER	-26	-22	-22	-22	-22	-22	-22	-22	-19
WATER OF URINE	921	818	349	395	273	154	936	1785	937
SP.GR. OF URINE	1.012	1.012	1.029	1.031	1.032	1.031	1.016	1.008	1.013
WATER OF STOOL	63	0	0	66	0	38	108	76	37
BLOOD	10	5	45	11	18	61	12	13	13
N.P.N. IN MG. PER 100 C.C.	32.9	32.2	36.0	37.7	41.0	41.7	34.3	31.1	31.3
WATER VAPORIZED	1040	1477	1687	1490	1016	545	1364	1237	1282
MAX. MOUTH TEMP. °F.	98.3	98.4	98.4	99.4	99.0	98.4	98.2	98.6	98.0
TOTAL AVAILABLE WATER	2097	2302	651	651	651	3039	3464	3211	2024
TOTAL WATER OUTPUT	2034	2300	2081	1961	1307	798	2420	3111	2269
WATER BALANCE	+63	+2	-1430	-1311	-656	+2241	+1044	+100	-245

AMOUNT OF FLUID LOST IN DEHYDRATION PERIOD 3397 GRAMS
IN RELATION TO TOTAL BODY WEIGHT OF SUBJECT 59000 GRAMS = 5.8 PER CENT.

On April 22, the first day of the recovery period, R.M. drank 2392 Gm. of water. In spite of this, the water of the urine on this day was only 154 Gm. compared to 273 Gm. on the previous day, when no water was drunk. The answer to this apparent paradox was simple. The water balance figures for April 22 showed that the tissues took up 2241 Gm. of water to replace fluid lost during the dehydration period. This was corroborated by a weight gain for the day of 2256 Gm. Under these circumstances there was little water left for the kidneys, even though waste products normally excreted by them were accumulating in the blood. From these data, it is clearly evident that water for the restoration of body fluid is a "preferential process," that is, water will be used to satisfy this need before water becomes available for kidney function. Thus in a dehydrated patient, a satisfactory urine output will be obtained only when the preferential processes—water for the restoration of body fluid and water for vaporization from the skin and lungs—have been taken care of.

On the second day of the recovery period, April 23, the water balance figures showed a hydration of only 1044 Gm. When this amount is subtracted from the total available water of 3464 Gm., sufficient is left to take care of all of the other water using processes and leave enough for 936 Gm. of urine water. With this water the kidneys were able to

excrete most of the previously retained waste materials, the blood nonprotein nitrogen falling to within 2 mg. per 100 cc. of the preliminary period level. With the fluid depletion already restored, the water balance for April 24 and 25 showed normal exchanges.

The Amount of Fluid lost To Produce Serious Dehydration.—The determination of this point was the primary object of the investigation. As far as could be told from clinical observations and particularly from the rise in the nonprotein nitrogen of the blood, the dehydration was carried out to the same degree in both subjects and was about as severe as they could tolerate. In Table I the fluid loss of 4053 Gm. by J.N. amounted to 5.7 per cent of his total body weight. For R.M., Table IV, the fluid loss of 3397 Gm. amounted to 5.8 per cent of his total body weight. The difference in the ages of the adult subjects did not affect the results. The figures seem to be remarkably consistent, but are not surprisingly so considering the close correlation of other biologic facts in different individuals and even between different species.

Because it was more simple, we presented the loss of body fluid in terms of per cent of total body weight rather than in per cent of total body water. Considering the total water content of the body to be 65 per cent of the total weight and recalculating our figures, J.N.'s serious effects were due to a loss of 8.7 per cent of his total body water and R.M.'s similarly to a loss of 8.8 per cent. These results are in entire accord with the data from the experimental dehydration of animals by Balcar, Sansum and Woodyatt,[6] Nothwang,[7] Keith[8] and Rubner,[9] the latter stating that an animal can lose scarcely 10 per cent of its water content without serious consequences.

Water Balance of a Dehydrated Patient.—The following is an account of a water balance study on a patient who entered the hospital in a condition of dehydration which appeared clinically to be of about the same degree as that produced in the experimental subjects. The study began two hours after the patient's admission to the ward and was continued until the water balance was back to normal. We were particularly interested in knowing whether the recovery from dehydration followed along the same lines as that of the experimental subjects and just what the fluid loss had been in relation to the patient's total body weight.

SUMMARY OF CASE.—B.L., a woman of 48 years of age, was admitted to the surgical ward on March 29, 1935, with a complaint of abdominal pain and distention, and obstipation of 48 hours' duration. Vomiting had occurred twice during that time. No food or fluid had been taken in the 30 hours previous to admission. The past history revealed a lower abdominal operation 12 years previously for intestinal obstruction. On May 26, 1934, a left pyelolithotomy and nephrostomy had been done for stones and on June 20, 1934, a right nephrectomy was performed for a calculus pyonephrosis.

On physical examination the patient appeared to be in moderate pain and was definitely dehydrated. Her lips were dry and her tongue showed only a slight amount of moisture at the edges. The abdomen was moderately distended, was tympanitic and tender in the lower half. On admission the leukocyte count was 19,000 per cc. of blood and the hemoglobin was 104 per cent (Sahli). No urine could be obtained on catheterization. The nonprotein nitrogen was 61.2 mg. per 100 cc. of blood. The blood chlorides were 558 mg. per 100 cc. (plasma). A flat roentgenogram of the abdomen showed a distention of what appeared to be isolated lops of small bowel.

In view of the damaged remaining kidney, the dehydration, the oliguria and the high value for the blood nonprotein nitrogen, a decision was made to treat the obstruction conservatively for the time being. The patient was made comfortable with opiates. A Wangensteen duodenal suction apparatus was started and heat was applied to the abdomen. Intravenous fluids were given by one of us who stayed in the room with the patient during the day. An assistant stayed with the patient during the 12 hour night period. In this way the abdominal condition was closely followed and the water exchange accurately determined. During the time of our observation the abdominal condition did not materially change.

The water balance of the patient during the three and a half days of the hydration period is shown in Table V. The important consideration in the water requirements of this patient was that sufficient fluid be available for all the preferential process, that is, water for vaporization and for the restoration of the tissue deficit, plus an excess permitting

TABLE V

Water balance during hydration of patient B.L.

DATE. 1935	MAR.29	MAR.30	MAR.31	APR. 1
WEIGHT IN GRAMS OF:	12 HOURS			
INTRAVENOUS FLUID	3977	3912	6565	4915
RETAINED ENEMA FLUID	0	0	718	0
WATER OF OXIDATION	150	350	300	275
PREFORMED WATER	100	220	200	200
URINE	31	406	4884	4598
SP.GR. OF URINE	1.020	1.013	1.011	1.006
BLOOD N.P.N. MG. PER 100 C.C.	63.8	73.5	48.3	37.9
STOOL	0	0	7	0
BLOOD	0	10	12	6
SPUTUM	0	0	30	0
GASTRIC DRAINAGE	161	306	120	0
INSENSIBLE LOSS	595	2470	1665	1586
MAX. MOUTH TEMP. °F.	100.5	102.3	98.4	100.0
TOTAL AVAILABLE WATER	4227	4482	7783	5390
TOTAL WATER OUTPUT	787	3192	6718	6190
WATER BALANCE	+3440	+1290	+1065	-800
AMOUNT OF FLUID RESTORED IN HYDRATION PERIOD 4995 GRAMS IN RELATION TO TOTAL BODY WEIGHT OF PATIENT 82000 GRAMS = 6.1 %.				

a fairly large urine output. The following phases of her water exchange were of particular interest.

Intravenous Fluid.—Because the patient was in need of water and showed only a slight decrease in blood chlorides at the time of her admission, the intravenous fluid given was a 5 per cent glucose solution with the exception of 1559 Gm. of physiologic saline solution on April 1. This salt solution was given because on the latter part of the previous day the blood chlorides were down to 437 mg. per 100 cc. (plasma). This choice of fluid for parenteral administration was in accordance with our opinion that the way to supply an abundance of available water to the body is to give a 5 per cent glucose solution. The glucose is oxidized and the water is left for all purposes. A saline solution is given only when sodium or chloride ions are needed, as shown by and followed by blood chemistry studies. An excess of salt solution may be the cause of edema. The glucose solution readily restored the depleted body fluids of this patient.

Water Balance of First and Second Day of Hydration.—These two days are considered together because they had several features in common. The data shown for March 29 ran from 8 P.M. to 8 A.M. the following morning, and thus covered only the latter 12 hours of the usual 24 hour period. During the 36 hours of March 29 and 30, the total available water amounted to 8709 Gm. Most of this water came from 7889 Gm. of intravenous fluid. In spite of this fairly large supply of fluid, the urine output for this period amounted to only 437 Gm. At the specific gravities shown for this urine, only a small amount of waste material could be excreted, and as a result the nonprotein nitrogen of the blood increased from 61.2 mg. per 100 cc. at the time of admission to 73.5 mg. The maximum concentration of the urine to a specific gravity of only 1.020 under the conditions of dehydration present was well below the normal of 1.029 to 1.032 and was definite evidence of impaired kidney function.[5] The question of whether a calculus obstruction of the only remaining ureter might be responsible for the low urine output of 437 Gm. was raised, but was quickly abandoned when the other water losses of the period and the experience from the dehydrated subjects was considered. We have frequently emphasized the fact that the kidneys do not have the privilege of taking a share of the total available water for their work, but function with the water left after all the other water using processes have been cared for. An inspection of the water exchange for the 36 hour period showed that the low urine volume here was no exception to the rule. The total amount of available water was 8709 Gm. The insensible vaporization of water is a preferential process which took 3065 Gm. The studies on the subjects J.N. and R.M. showed that water to the tisues to replace depleted body fluids is also a preferential process. In this instance it amounted to 4730 Gm. The sum of the water vaporized and the water to the tissues was 7795 Gm. From the 8709 Gm., this left only 914 Gm. of water for other purposes. Subtracting from this the 467 Gm. fluid loss in gastric drainage and little was available for the kidneys. The low output of urine was not the fault of the patient, or the patient's kidneys. We had taken over the job of supplying a satisfactory amount of available water and although 7889 Gm. of a 5 per cent glucose solution were given intravenously the amount was inadequate to meet the actual water requirements.

Water Balance of Third and Fourth Day of Hydration.—Profiting by the experience of the first two days of the hydration period, the total supply of available water for the third day was stepped up to 7783 Gm. by increasing the intravenous fluid to 6565 Gm. The tissue thirst having been largely cared for on the two preceding days the water balance showed the hydration to amount to only 1065 Gm. The insensible loss of water was 1665 Gm. When the total of these two factors is subtracted from the total available supply, 5053 Gm. of water is left for other purposes. The gastric drainage, the blood, and the stool loss was small, so the urine volume was 4884 Gm., and the blood nonprotein nitrogen was reduced to 48.3 mg. per 100 cc.

Since the water exchange of March 31 was entirely satisfactory the same plan of treatment was carried out on April 1. Intravenous fluids of 4915 Gm. provided a large part of the 5390 Gm. of available water. A negative water balance showed that an additional 800 Gm. of water previously taken up by the tissues also became available. As a result, after accounting for the insensible loss of water, the urine output was 4598 Gm. and the nonprotein nitrogen of the blood was down to a normal level.

Fluid Lost by Patient to Become Dehydrated.—The water balance figures of Mrs. B.L. for the three and a half days showed a hydration of 4995 Gm. This represented the amount of water added to her body to restore tissue fluids. There is every reason to believe that it represented the quantity of fluid lost by the patient in becoming dehydrated. This quantity amounted to 6.1 per cent of her total body weight. This was a close correlation with the 5.7 and 5.8 per cent loss by the experimental subjects.

COMMENT

Dehydration of varying degrees is commonly seen in sick individuals, and restoration of the depleted fluids is one of the first considerations in their

treatment. Because in many surgical conditions there is an interference with the normal ingestion of water, the hydration of these individuals is dependent upon the parenteral administration of fluid, and therefore is governed by the surgeon. If it were known how much fluid is lost to produce serious effects, in the calculation of water needs an allowance could be made for the water to restore body fluid in a fairly accurate quantitative manner.

To investigate the problem, the first requirement was some measure of dehydration to serious effects. When the total output of water is greater than the supply, the kidneys only get whatever water is left over after all the other channels of exit have been satisfied. Since a definite minimum amount of water is needed by them to excrete every gram of solids,[10] retention of urinary wastes is an important result of a deficient supply of water. Retention is prevented for a time by a release of body water. When it is more important for the organism to keep what water it has rather than to furnish the kidneys with amounts needed by them to carry out their full function, urine wastes begin to accumulate. This point may be properly regarded as the beginning of serious dehydration. Its presence can be shown in a somewhat quantitative manner by a rise in the nonprotein nitrogen of the blood to abnormal values.

From a water balance study involving the dehydration of two normal adult subjects and the hydration of a patient who showed moderately severe effects of depleted body water, it was apparent that with a loss of body fluid amounting to about 6 per cent of the total body weight an individual is at the beginning of serious dehydration. At this point, the clinical signs of dehydration will be well established; the blood will be concentrated, and the urine output insufficient to maintain normal kidney function so that the nonprotein nitrogen of the blood will be above normal. The effort of the kidneys to rid the body of waste materials under the adverse circumstances may result in kidney damage, as shown by the occurrence of protein, casts and erythrocytes, in the urine. All of these findings indicate the urgency of a plentiful supply of water in as short a time as possible.

For our subjects only water was needed to replace the depleted body fluids. This is not the usual condition in dehydrated patients.[11] Many of them, as by vomiting, will have lost water and the materials normally held by it in solution, chiefly sodium and chloride ions. These losses will be shown by appropriate blood chemistry studies. A sodium chloride solution must then be given, but only until the blood studies show the loss of these electrolytes to have been corrected. Many times on an active surgical service fluids are given intravenously, not to treat dehydration, but to prevent dehydration. The patient, often as a result of an operation, is not permitted to or cannot drink sufficient water. Water is needed to maintain a normal water balance, but there is no need for sodium chloride and an excess of salt solution may be the cause of edema. If a 5 per cent glucose solution is given to these patients, the glucose will be oxidized and the water left available for all purposes.

The important fact in the recovery of our subjects from dehydration was

that the tissues took nearly all of the first water given to replace lost body fluid. This fact is readily applicable to the treatment of dehydrated patients. From previous studies[12, 4] we emphasize that a fairly accurate calculation of the amount of fluid needed to maintain a satisfactory water balance in any given patient can be made by the following allowances:

(1) Water for urine: At least 1500 cc. per day for the sick surgical patient.

(2) Abnormal losses: Such as vomitus or drainage from intestinal or biliary fistulae. These losses should be measured and the amounts recorded on the patient's chart.

(3) Water for vaporization from the skin and lungs: This will vary from 1000 to 1500 cc. per day for the simple uncomplicated surgical case. With the increased heat production of fever or hyperthyroidism, or the sweating of hot and humid environments, this loss will amount to from about 1500 to 3000 cc. per day with a safe average of two liters a day.

If, for the dehydrated patient, only the above three channels of water loss are considered, the tissues will take water for the restoration of normal fluid content and the kidneys will suffer accordingly. Therefore, for the dehydrated patient an additional allowance must be made:

(4) Water for the restoration of depleted body fluids: For patients showing the beginning signs of serious dehydration—a dry tongue, scanty urine, blood nonprotein nitrogen increased—a fair estimation of this water need can be made on the basis of 6 per cent of the total body weight. Examples for individuals of various weights would be as follows:

Weight of patient Kg.	6 per cent Gm. or cc.
100	6000
80	4800
60	3600
40	2400
20	1200

Lesser and greater degrees of dehydration than that produced by us are commonly met with in sick individuals.[13, 14] From experience, we have been able to estimate the degree of their dehydration on the basis of the findings in our subjects and thus to vary the 6 per cent figure to fit the individual need.

From these calculations of water requirements, it is clearly evident that for the dehydrated patient the usual two or three liters of fluid are entirely inadequate, in many instances from six to nine liters being actually needed. In our hands, the management of the water balance of the sick patient by figures based on facts has yielded gratifying results.

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